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December 1946

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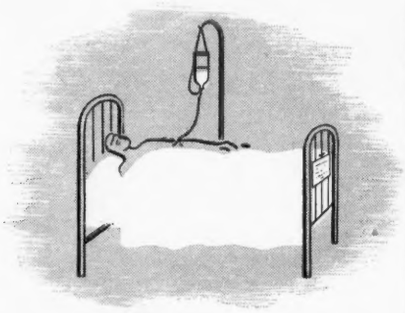

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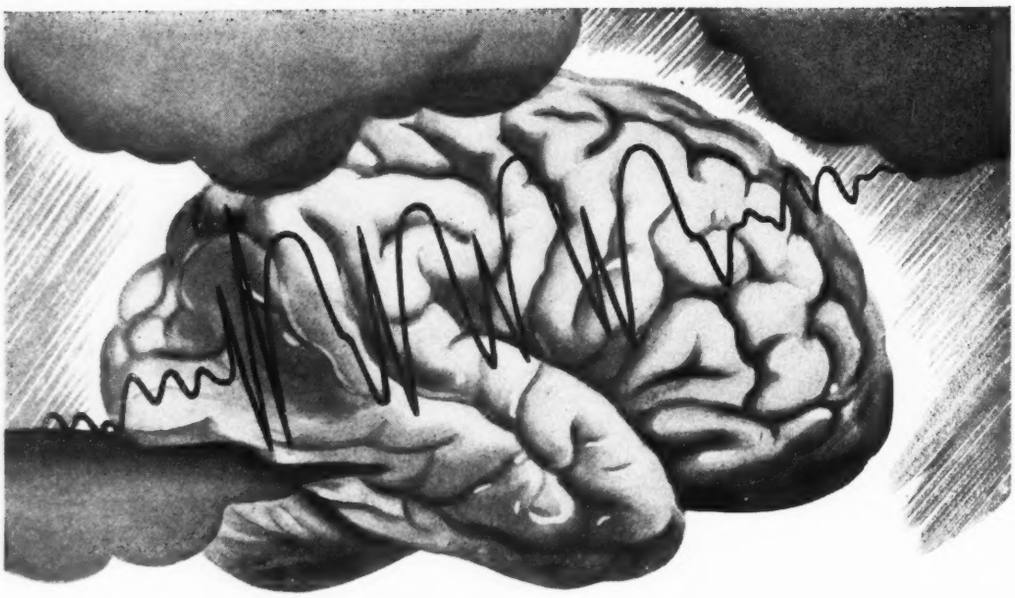

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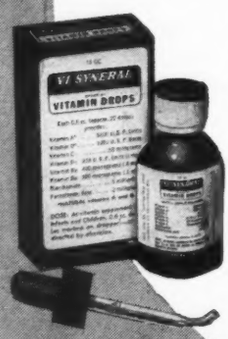

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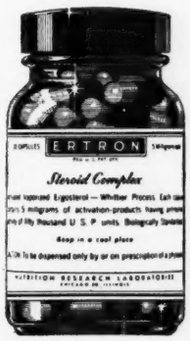

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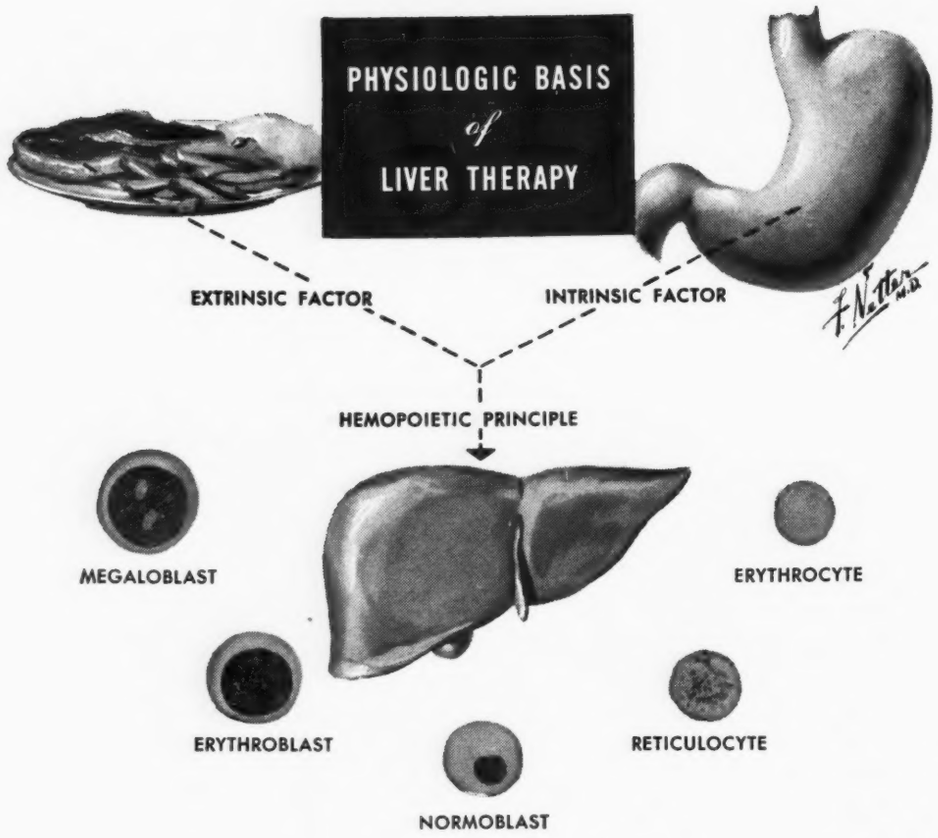

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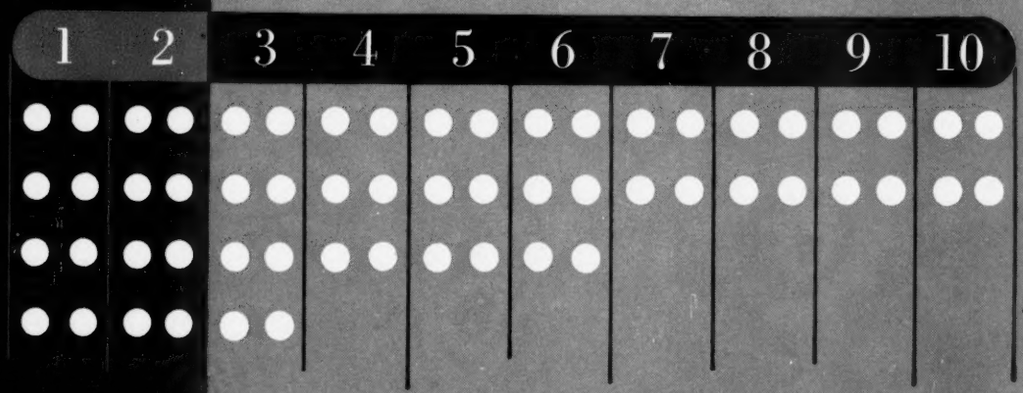

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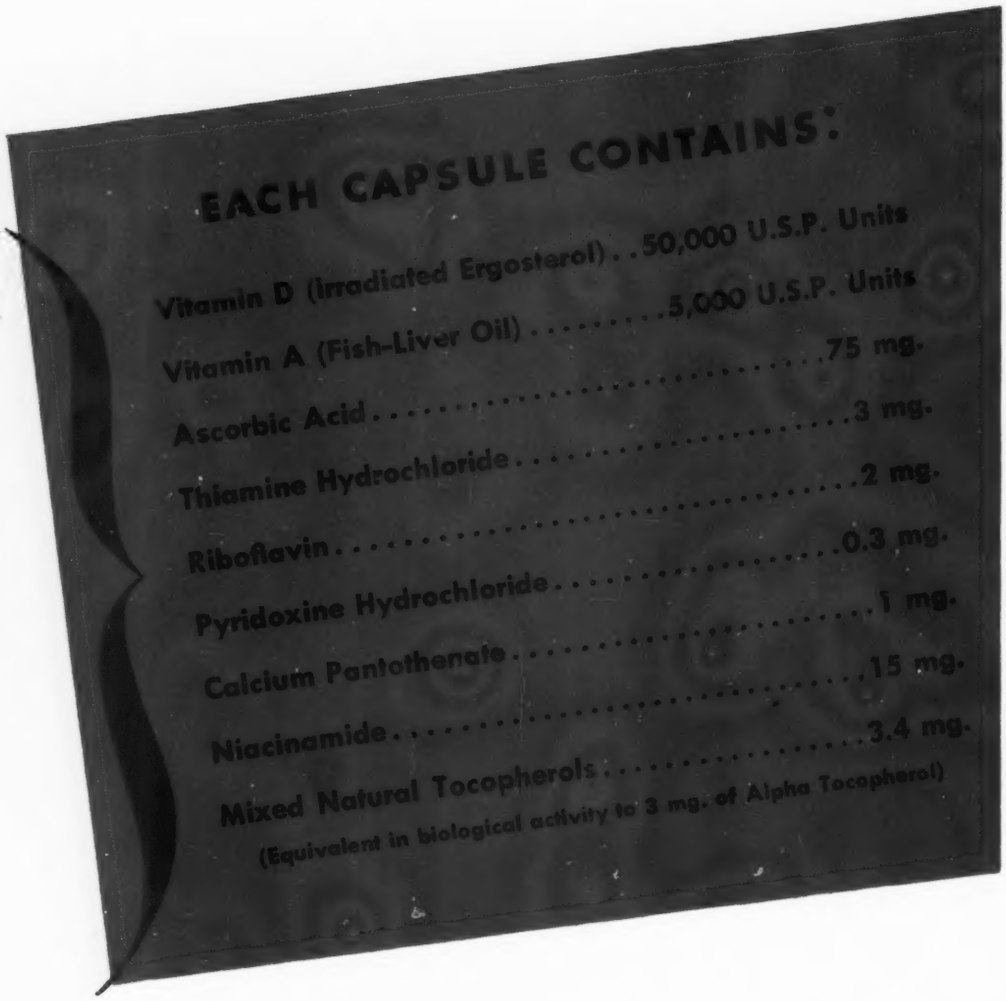
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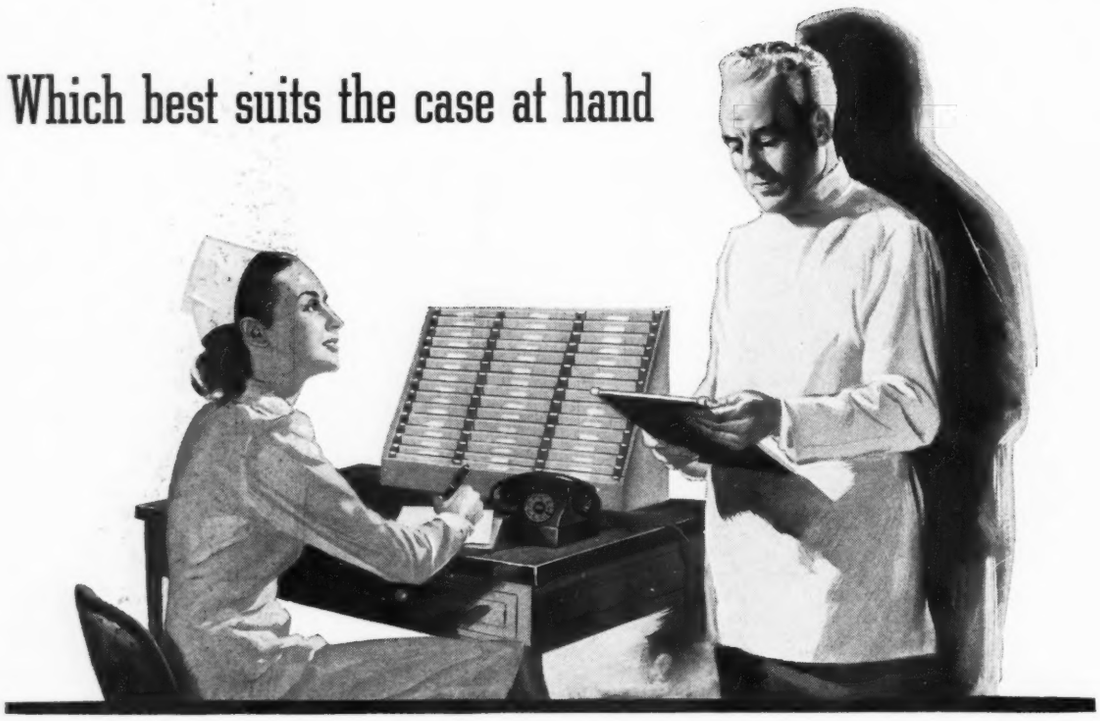

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The American Journal of Medicine

VOL. 1 DECEMBER, 1946 No. 6

Studies on Chronic Thyrotoxic Myopathy*

GEORGE W. THORN, M.D. *and* HOWARD A. EDER, M.D.

BOSTON, MASSACHUSETTS

MUSCULAR weakness is a common accompaniment of thyrotoxicosis, and it is well known that many patients with severe thyrotoxicosis manifest striking impairment in muscular function.[1] There are, in addition, patients with thyrotoxicosis in whom the signs and symptoms of muscular weakness may be entirely out of proportion to the degree of thyrotoxicosis. In some of these patients the usual clinical signs of thyrotoxicosis may be so slight or obscure as to be overlooked. These instances, although not common, merit consideration because of the striking improvement in muscular strength and development which may follow treatment of the underlying thyrotoxicosis.

Starling, Darke, Hunt and Brain[2] have suggested the following classification of myopathies associated with thyrotoxicosis: (1) Exophthalmic ophthalmoplegia; (2) thyrotoxic myopathy, (A) acute thyrotoxic myopathy, (B) chronic thyrotoxic myopathy, (C) thyrotoxic periodic paralysis; and (3) myasthenia gravis and thyrotoxicosis.

Exophthalmic ophthalmoplegia[2,3] is a disorder localized in the soft tissues and muscles of the orbits. It frequently persists after thyroidectomy and in some instances actually progresses postoperatively. Recent studies by Rundle and Pochin[4] suggest that the exophthalmos is due to an increased fat content of the retrobulbar tissues. Severe generalized muscular disease has rarely been noted in patients with this condition.[2]

Acute thyrotoxic myopathy as described by Heuer[5] in 1916 appears to be a rapidly progressive myasthenia with involvement of the bulbar muscles as well as of the muscles of the limbs and trunk. It is usually fatal in one to two weeks, and death occurs most frequently from respiratory paralysis. In the case described by Heuer the differentiation from myasthenia gravis was made largely on the basis of response to faradic stimulation. It is questionable whether these cases represent a distinct entity rather than thyrotoxicosis associated with myasthenia gravis.

Thyrotoxic periodic paralysis not uncommonly occurs in conjunction with familial periodic paralysis. This condition should be distinguished from chronic thyrotoxic myopathy by the fact that patients are asymptomatic between attacks and their muscles appear to be normal. To date, thirty-five such cases have been described (Talbott[6]). In some instances thyroidectomy may cause a complete remission of symptoms (Dunlop and Kepler[7]), while in others there was merely a decrease in the frequency of attacks (Morrison and Levy[8]). The association of changes in serum potassium concentration with attacks of periodic paralysis is well known.[9] The mechanism whereby excessive thyroid hormone affects the disease is not understood.

Chronic thyrotoxic myopathy is one of the most important muscular disturbances associated with hyperthyroidism. It is char-

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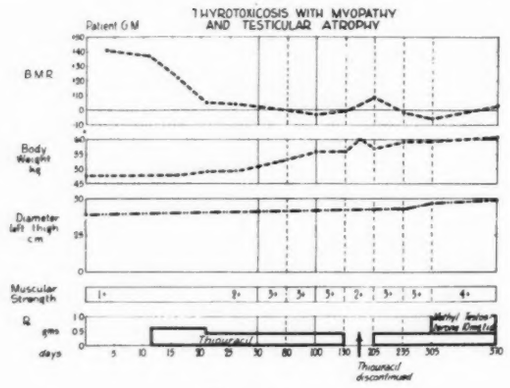

CHART 1.

acterized by marked muscular atrophy which is symmetrical and most frequently involves the shoulder and pelvic girdles. It was first described in 1895 by Bathhurst.[10] The literature has recently been summarized by McEachern and Ross[11] who have reported thirteen such cases including three of their own.

We wish to report five additional cases of this disease which were seen over a relatively short period at the Peter Bent Brigham Hospital and to emphasize the importance of recognizing these cases because of the dramatic improvement which may follow correction of the underlying thyrotoxicosis.

CASE REPORTS AND OBSERVATIONS

The principal features in the five cases of chronic thyrotoxic myopathy are summarized in Table 1.

CASE 1. A fifty-year old male presented generalized muscular weakness with striking atrophy of the muscles of the shoulder girdle. Signs of thyrotoxicosis were minimal; gonadal atrophy was present. The patient made an excellent response to thiouracil therapy supplemented later with methyl testosterone. (Chart 1.)

G. M., No. M65090, a fifty-year-old Italian mill worker, entered the Peter Bent Brigham Hospital on October 6, 1943, because of marked weakness. For thirty years the patient had tolerated warm weather poorly. He had always been comfortable in cold weather and frequently slept only with a sheet, even in cold weather. During the seven months before admission these symptoms became more pronounced, and, in addition, he had noted marked muscular weakness, especially of his legs. For eight weeks this had been so pronounced that he had been unable to climb stairs and spent most of his time in bed. During this period he had noted rapid heart action, and ankle edema had occurred at the end of the day. He had lost approximately 30 pounds, and his appetite had not been as good as usual.

The patient's family history was non-contributory, and his past history was not noteworthy except for a marked decrease in potency.

Physical examination on admission showed a middle-aged, dark Italian lying quietly in bed with a slight amount of restlessness. His temperature was 98°F., pulse 104, respirations 16 and blood pressure 140/70 mm. Hg. His skin was warm but not moist except in the palms. There was marked muscular atrophy, especially in the muscles of the shoulder girdle with marked winging of the scapulae and marked atrophy of the supraspinatus and biceps muscles. There was also atrophy of the legs, especially of the quadriceps. Muscles of the forearms and lower legs did not show such marked atrophy. There was no fasciculation. His gait was unsteady; he walked with a broad base and was unable to climb stairs at all. He did not have exophthalmos or other eye signs. There was a definite fine tremor to the tongue and outstretched hands. The thyroid was enlarged but contained no nodules, and a bruit could be heard over it. The lungs were normal. The heart was not enlarged, the sounds were forceful, and there was a grade 1 systolic murmur at the apex. The abdomen was normal. The genitalia were small with small testes, and the prostate was also small. There was slight pitting edema of the ankles. Neurological examination showed nothing abnormal except the muscular weakness. Reflexes were physiological.

Laboratory examination revealed the following: Blood serology was negative. Urine specific gravity was 1.015 with no protein or sugar. Sediment contained many white cells. Hemoglobin was 12.2 Gm. per cent, hematocrit 35 per cent, and sedimentation rate 22 mm. per hour (method of Wintrobe). The white blood count was 8,250, and smear appeared normal.

TABLE I

THYROTOXIC MYOPATHY

Patient	G. M. Case I	M. S. Case II	E. M. Case III	J. B. Case IV	Y. C. Case V
Sex and age	Male, 50 years	Male, 40 years	Female, 43 years	Female, 56 years	Female, 22 years
Duration of symptoms	7 months	2 months	6 months	6 months	6 months
Thyroid enlargement	+	+	++	0	++
Eye signs	None	Lid lag	Stare, lid lag	None	Exophthalmos, stare, lid lag, impaired convergence
Tremor	+	+	++	0	+
Muscular involvement	Generalized weakness and atrophy, most marked in shoulder girdle	Generalized weakness with atrophy especially in arms	Generalized weakness and atrophy; regurgitation of fluids	Extreme generalized weakness and atrophy	Generalized weakness; atrophy especially in upper arm
Fasciculation	0	0	0	0	0
Initial basal metabolic rate—%	+37	+40	+60	None taken	+33
Spontaneous creatinuria mg./24 hours	100	200	590	Not done	420
Creatine tolerance test* % retention of ingested creatine	62	28	Not done	Not done	Not done
Urinary 17-ketosteroids mg./24 hours	8.3	8.6	2.7	Not done	9.4
Cardiac enlargement by *x*-ray —%	0	0	+25	0	+10
Circulation time—seconds**	9	Not done	11	Not done	14
Prostigmine test	No improvement	No improvement	No improvement	Not done	No improvement
Treatment	Thiouracil for 1 year; methyl testosterone for 2 months	Subtotal thyroidectomy; methyl testosterone; testosterone propionate for 4 months	Thiouracil for 9 months; thyroidectomy	Iodine for 2 days	Thiobarbital for 5 months
Result	Strength returned almost to normal	Strength returned to normal until onset of hypothyroidism	Strength returned almost to normal	Died	Good return of strength
Basal metabolic rate after treatment	−3% (18 months)	−22% (6 months)	+20% (18 days)	.....	−3% (5 months)

* Normal for males 85–100% retention; normal for females 80–95% retention.

** Decholin, arm to tongue; normal 15–18 seconds.

Blood urea nitrogen was 11 mg. per cent, nonprotein nitrogen 37 mg. per cent, total protein 6.2 Gm. per cent, albumin 4.0 Gm. per cent, globulin 2.2 Gm. per cent, fasting blood sugar 99 mg. per cent, blood cholesterol 175 mg. per cent, calcium 5.6 m.M. per liter, phosphorus 1.56 m.M. per liter, and alkaline phosphatase 3.7 Bodansky units. Stool examination was normal. Arm to tongue circulation time (decholin) was 9 seconds. Prostigmine test showed no increase in muscular strength after administration of 1.5 mg. of prostigmine subcutaneously.

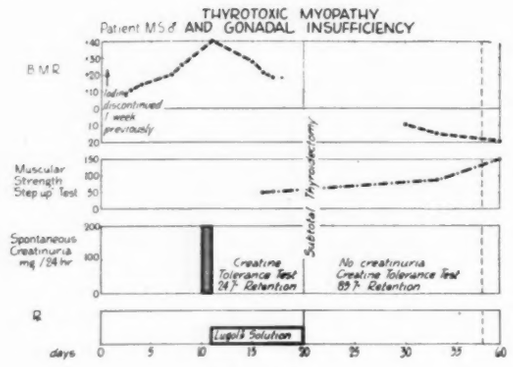

CHART 2.

Sulkowitch test for calcinuria was 4+. He excreted 0.100 Gm. of creatine per twenty-four hours. Creatine tolerance test showed retention of only 62 per cent of ingested creatine (normal 85 to 100 per cent retention). The hippuric acid test showed 1.17 Gm. excretion in one hour. Urinary 17-ketosteroid output was 8.3 mg. per twenty-four hours. The electrocardiogram was normal. *X*-ray films of the heart showed no apparent enlargement; the lungs were clear and there was no substernal thyroid. The basal metabolic rate before treatment ranged from +50 to +37 per cent.

The patient's metabolic rate dropped from +50 to +37 per cent on bed rest. (Chart 1.) On the tenth hospital day he was started on 0.6 Gm. of thiouracil daily. This was maintained until discharge, thirty-three days later. His basal metabolic rate fell steadily and after eleven days of treatment was +5 per cent. He showed no marked improvement in muscular strength, however, until shortly before discharge when he was able to walk up stairs without holding onto the rail. Strength of his hands tested with a dynamometer showed no appreciable increase. Symptomatically he felt much better. He no longer complained of sweating. His appetite was improving, and he gained 1.2 kg. in the hospital. The creatine tolerance test at time of discharge showed that he retained 96 per cent of the ingested creatine. He was followed in the metabolic clinic where his basal metabolic rate ranged from +4 to −3 per cent. His weight steadily rose so that on February 15th he weighed 59 kg. and his weight remained at this level. The change in appearance of his muscles at this time was striking. There was no longer any evidence of muscular atrophy, and he was able to climb stairs with ease. On March 28th he complained of swelling of his face and arms (myxedema), and thiouracil was discontinued for a month. It was then resumed. His basal metabolic rate ranged from −2 to +6 per cent, and his weight remained constant. He still felt that he did not have complete return of muscle strength. Although he had returned to work, he could not do as heavy work as he could before this illness.

He was readmitted to this hospital on August 8, 1944, for re-examination. Physical examination showed striking increase in the size of his muscles, and this was corroborated by measurements. The thyroid was no longer palpable; the heart was not overactive, and the testes were atrophic as previously described. Basal metabolic rate was −5 per cent. He excreted 0.74 Gm. of creatinine and 0.23 Gm. of creatine per twenty-four hours. The Wilder test was negative. His urinary 17-ketosteroid excretion was 10.1 mg. per twenty-four hours. He was able to do 5166 foot-pounds of work using the step test. He was discharged on 30 mg. of methyl testosterone daily.

On this medication he felt definite increase in strength, almost to complete restoration of normal. His potency increased so that he was able to have satisfactory intercourse. After one month he stopped testosterone. During the following month his strength continued to improve until he felt as strong as before his illness. His potency, however, diminished. Physical examination on October 17, 1944, showed increase in weight of 2 kg. and increase in size of his muscles. There was no further increase in muscle strength by the step-up test.

CASE II. A forty-six-year-old male complaining of generalized muscular weakness, involving particularly the right arm, showed atrophy of both arms. The patient also had testicular atrophy. Signs of thyrotoxicosis were minimal. The patient's muscular strength responded strikingly to iodine therapy followed by subtotal thyroidectomy and subsequently supplemental testosterone therapy. (Chart 2.)

M. S., No. M64175, a forty-six-year-old salesman, entered the Peter Bent Brigham Hospital on May 11, 1943, because of marked muscular

weakness for two months. He had been in good health until six months prior to admission when he noted a choking sensation on swallowing with a sense of fullness in his epigastrium. On a regimen of atropine and aluminum hydroxide, these symptoms had subsided. Two months before admission he had begun to feel tired and noted weakness of his muscles with difficulty in walking. In the week prior to admission the slightest exertion had caused him to break out in a cold sweat with a generalized aching in his bones and muscles. During the previous month he had lost 18 pounds despite the fact that his appetite had been as good or better than before. In addition, he had noted some palpitation, nervousness, a tendency to sweat easily and a slight tremor of his hands. He had been placed on Lugol's solution by his local physician and had continued this up to four days prior to admission. The remainder of the patient's past history and his family history were non-contributory.

Physical examination on admission showed a well nourished, white male who was very restless and nervous. His temperature was 99°F., pulse 90, respirations 20 and blood pressure 130/80 mm. Hg. His weight was 64 kg. He showed generalized muscular weakness of a mild degree, somewhat greater in his right arm than in his left, with some loss of muscle substance on the right. His reflexes were normal. The skin was warm and of fine texture, and he was sweating freely. His hair was normal in distribution and appearance. The eyes were not unusually prominent, but there was slight lid lag. There was a fine tremor of the tongue. Thyroid was slightly enlarged with a slight bruit over the right lobe. The lungs were clear, the heart was not enlarged, and sounds were not hyperactive. There was a grade I systolic murmur at the apex. The abdomen was not remarkable and there was no significant tremor of the hands. His testes were small, and his prostate was soft.

Laboratory examination revealed the following: Blood serology was negative. Urine specific gravity was 1.012, no protein or sugar. Sediment was negative. Hemoglobin was 13.5 Gm. per cent, hematocrit 42 per cent, sedimentation rate 6 mm. per hour. White blood count was 9,000 with 58 per cent neutrophils and 38 per cent lymphocytes. The red cells appeared normal. Blood urea nitrogen was 10 mg. per cent. Total protein was 6.3 Gm. per cent, albumin 3.2 Gm. per cent, globulin 3.1 Gm. per cent. Fasting blood sugar was 115 mg. per cent, carbon dioxide combining power 25.8 m.M. per liter, serum chloride 97 m.Eq. per liter, cholesterol 149 mg. per cent, urine 17-ketosteroids 8.6 mg. per twenty-four hours. The stool was normal. While on a creatine-free diet he excreted 0.201 Gm. of creatine in twenty-four hours. He retained only 28 per cent of the ingested creatine (2.6 Gm.) in the creatine tolerance test. The electrocardiogram showed normal curves and the chest film was normal. The gastrointestinal series was normal except for pylorospasm, and the barium enema was also normal. After 1.5 mg. of prostigmine subcutaneously, he showed no increase in muscular strength. His initial basal metabolic rate was +11 per cent.

During his hospital stay he ran a low-grade fever while on bed rest. (Chart 2.) His basal metabolic rate gradually rose from +11 to +40 per cent on his eleventh hospital day. (He had been on Lugol's solution before admission.) He was then placed on Lugol's solution and in six days his basal metabolic rate fell to +19 per cent, his creatine excretion dropped to 0.015 Gm. per twenty-four hours, and subtotal thyroidectomy was performed. The gland showed hyperplasia with iodine involution. After operation his basal metabolic rate continued to drop and was −14 per cent on June 10th, at the time of discharge from the hospital. After operation he had no spontaneous creatinuria, and he retained 84.4 per cent of the ingested creatine in the tolerance test. His strength rapidly increased. Before operation he could step up and down on the 12-inch step for only 50 seconds; after operation he was able to go for 88 seconds. One month after operation he was able to do this work for 150 seconds. After returning home his strength improved. He gained 10 kg. and was able to return to work. He continued in good health until October, 1943, when he began to feel fatigued and began to note slowness of action and thought. His basal metabolic rate fell to −20 per cent, and he was readmitted in November, 1943, with signs and symptoms of myxedema. His cholesterol at that time was 500 mg. per cent.

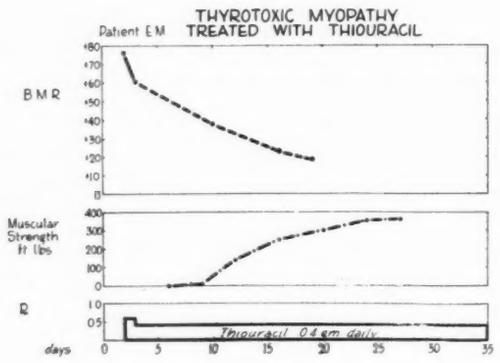

CHART 3.

Creatine tolerance test showed retention of 84 per cent of the ingested creatine. He was somewhat weaker and was able to raise himself on the 12-inch step for 90 seconds. He was started on 60 mg. of thyroid daily and has since lost his signs of myxedema.

After discharge he still complained of some muscular weakness although there was no evidence of atrophy. Since it had been noted that his testes were small, prostate soft, and libido was absent, he was started on 30 mg. of methyl testosterone daily. After one month he showed appreciable improvement and was able to work ten hours a day. The following month he received testosterone propionate 25 mg. daily for three days and bi-weekly thereafter. On this medication his strength returned completely to normal, and he was able to work on the step for 115 seconds.

CASE III. This was a forty-three-year-old female with extreme muscular weakness and generalized muscular atrophy. Signs of thyrotoxicosis were clearly evident. Treatment with thiouracil resulted in a prompt and striking improvement in muscular strength as well as in size of muscles. (Chart 3.)

E. M., No. M65818, a forty-three-year-old housewife, entered the Peter Bent Brigham Hospital on February 3, 1944, because of such extreme weakness that she had been unable to get out of bed for the previous three weeks. She had felt quite well until six months before admission when she had noted marked weakness of her arms and legs with fatigue after very slight exertion. This weakness had become progressively worse, and for several months she had been unable to climb stairs. For three weeks she had been too weak to get out of bed, and she said that exertion made the weakness more marked. For several months her speech had been thick. There had been occasional regurgitation of fluids into her nose, but she had had no diplopia. She had always been uncomfortable in hot weather. Since her present illness, her appetite had been poor and she had lost 30 pounds. In addition, she had become nervous and irritable and had noted palpitation. Her local physician had told her that her heart was irregular but that she had no symptoms of heart failure. Four months previously she had noted swelling of her neck but had had no hoarseness or difficulty in swallowing. Her physician had prescribed iodine which had been followed by marked relief of symptoms, but this therapy had not been continued. The remainder of the patient's past history was non-contributory.

The family history was of interest in that she had one sister with a goiter of three years' duration.

Physical examination on admission showed an extremely thin woman with evidence of marked weight loss. Her temperature was 98.6°F., pulse 106, respirations 32, blood pressure 130/64 mm. Hg. She was very weak and could not sit up unsupported. The skin of her face had a pinkish hue; her palms were warm and moist; and there was marked wasting of all muscles. Her eyes were prominent with a definite stare and lid lag. Retinal vessels were normal. She had a marked tremor of the tongue. The thyroid was visibly enlarged in both lobes, and there was a definite bruit. It was not nodular. She had definite tremor of the outstretched hands. Her lungs were normal; her heart was slightly enlarged; the sounds were forceful. There was a grade I systolic bruit at the apex and base. The liver could be felt below the costal margin. She had no enlargement of the spleen or kidneys. Her reflexes were normal. She had marked hypotonia of her muscles. Her speech was thick, but it did not become worse on continuous effort.

Laboratory data revealed her blood serology to be normal. Urine specific gravity was 1.024 with no protein or sugar; sediment was clear. Hemoglobin was 12 Gm. per cent, hematocrit

43 per cent, sedimentation rate 7 mm. per hour. White blood count was 7,700 with 71 per cent neutrophils. The smear appeared normal. Blood urea nitrogen was 9 mg. per cent. Total protein was 5.4 Gm. per cent, albumin 2.7 Gm. per cent, globulin 2.7 Gm. per cent. Nonprotein nitrogen was 29 mg. per cent. Fasting blood sugar was 96 mg. per cent. Serum cholesterol ranged between 128 and 242 mg. per cent. She excreted 0.59 Gm. of creatine in twenty-four hours. A throat culture showed Streptococcus (alpha) and Staphylococcus aureus. Circulation time was 11 seconds on admission (arm to tongue decholin). The chest film showed the heart to be 25 per cent above average. The lungs were clear, and there was no substernal thyroid. Bone films showed normal detail with no osteoporosis. An electrocardiogram showed auricular fibrillation with inverted T_4. Repeated electrocardiogram showed normal sinus rhythm with left axis deviation. Initial basal metabolic rates were +76 per cent and +60 per cent.

The patient was started on thiouracil 0.4 Gm. daily. (Chart 3.) On her fifth day of treatment her basal metabolic rate was +38 per cent. At that time she had her second attack of paroxysmal auricular fibrillation, the first being on the day of admission. She had normal sinus rhythm with sinus tachycardia at all other times. During her hospital stay her basal metabolic rate fell steadily until it was +20 per cent at the time of discharge. Her pulse rate decreased also and was 80 at the time of discharge, whereas it had been 110 on admission. Her circulation time (decholin) increased to 15 seconds.

The most striking changes, however, were in her strength. She was able to walk around, whereas on admission she could not even sit up in bed. Her muscle strength as tested by standard work showed a 64-fold increase. She was alert and wide awake. Her skin was less warm but she still had slight tremors. Her appetite improved markedly, although there was no weight gain. Her heart was regular; sounds were not especially forceful. The systolic murmur at the apex disappeared. The thyroid was slightly larger and more firm. The bruit was still present but was markedly diminished. She was discharged on her thirty-first hospital day to continue on thiouracil medication. When last heard from after two and one-half months she had gained 9 kg. and was up and around and able to do most of her housework.

Case IV. A fifty-six-year-old female with extreme weakness and generalized muscular atrophy, had practically no signs of thyrotoxicosis. Her progress in the hospital was rapidly downhill with death on the seventh hospital day. Pathological examination revealed hyperplasia of the thyroid, striking atrophy of the skeletal muscles and of the *glomerulosa layer* of the *adrenal cortex*.

J. B., No. M64553, a fifty-six-year-old colored housewife, was admitted to the Peter Bent Brigham Hospital on July 9, 1943, because of palpitation and progressive fatigability of three months' duration. For six months previous to admission it had been noted that the patient desired cool surroundings and preferred cold to hot weather. At that time she also had complained of generalized weakness. Later this had become so pronounced that even climbing a short flight of stairs had produced severe fatigue, compelling her to rest in a chair from five to fifteen minutes thereafter. Two months later, because of steadily increasing weakness, she had been forced to cease work as a dressmaker. At the same time she had noticed palpitation. She had been seen by her family physician who found a tachycardia of 110–128, and she had been slowly digitalized. Palpitation had persisted up to the time of admission. The weakness had gradually increased, and one week before admission it had become so severe that she had had to stay in bed all the time. Two days before admission, she had been so weak that she needed constant nursing attendance. She became dyspneic on the slightest exertion. Just prior to admission, it had been noted that her speech was thick and that she had difficulty in pronouncing her words. The patient had lost weight during this illness, but the exact amount was not known.

Her past history included an episode five years before admission of swelling, redness and tenderness of her left ankle and knee. A diagnosis of acute rheumatic fever had been made at that time. The family history was noncontributory.

Physical examination on admission revealed a drowsy colored woman showing evidence of marked weight loss. Her temperature was 100.6°F., pulse 108, respirations 22 and blood pressure 140/80 mm. Hg. She appeared lethargic and spoke in a slow lisping voice. In the middle of the interview she became dyspneic and exhausted and lapsed into sleep. Her skin was warm and dry. There was partial alopecia at the temples and frontal regions. There was no evidence of oculomotor weakness. The pupils were equal and reacted to light and accommodation. There was no exophthalmos or abnormal eye signs and the ocular fundi were normal. The tongue was coated, was not atrophic and was without fibrillary twitchings. Neck veins were not distended. The thyroid was small and palpable without an audible bruit. The lungs were emphysematous but without râles. The heart was not enlarged, and the rhythm was regular with many extrasystoles. There was a systolic murmur heard over the entire precordium, loudest at the base. The abdomen was normal. Extremities showed generalized muscle wasting, most marked in the forearms, hands, calves and feet. There were no fasciculations. There was marked muscular weakness. The patient was unable to hold her hands out in front of her for more than half a minute and was barely able to lift more than one leg off the bed at a time. The only reflexes obtained were hypoactive biceps and knee jerks.

Laboratory examination revealed the following: Urine was not remarkable except for a trace of protein. Blood serology was normal. Red blood count 5.0 million. Hemoglobin was 14.5 to 16.0 Gm. per cent, hematocrit 45 per cent, sedimentation rate 17 mm. per hour, white blood count 6,000 to 10,000 with 58 per cent neutrophils. Platelets were present in normal amounts; the smear appeared normal. Blood urea nitrogen was 13 mg. per cent and non-protein nitrogen was 20 mg. per cent. Total protein was 8.6 Gm. per cent with 3.4 Gm. per cent albumin. Fasting blood sugar was 117 mg. per cent, carbon dioxide combining power 30.8 m.M. per liter, serum chloride 100 m.Eq. per liter. Spinal fluid was clear and colorless. No cells were present, and the dynamics were normal. Hinton and gold sol were negative. Electrocardiogram showed a sinus tachycardia with a ventricular rate of 120. There were premature auricular beats, left axis deviation, inverted T_1 and T_4 and a slightly elevated ST_4.

The patient ran a rapidly downhill course with a gradual rise of temperature, pulse and respiration rate. On the second day she was much more drowsy and the weakness was much more striking than on admission. She spoke with a thick voice and enunciation was poor. At no time, however, was there facial or hypoglossal paralysis. A chest film showed the heart to be normal in size and shape with some blunting of the left costophrenic angle. The heart beat was rapid and of small amplitude. On the fifth hospital day her temperature rose to 104.3°F., pulse to 100, respirations to 40. From this point on she was continuously stuporous, incontinent and required parenteral fluid administration. On the fifth day she also received 10 drops of Lugol's solution. The following day she received 1 Gm. of sodium iodide, 5 Gm. of sodium sulfadiazine, and 3 cat units of digitalis intravenously. This did not alter her course. Her temperature rose to 107.2, with a pulse of 168, and she died on her seventh hospital day.

Postmortem examination showed the thymus to be enlarged; it weighed 26 Gm. The heart weighed 340 Gm. and appeared normal. The abdominal viscera appeared normal except for a small argentaffinoma in the cecum, healed salpingo-oophoritis and a small leiomyoma of the uterus. The liver weighed 1,100 Gm. The kidneys were normal. The adrenals grossly were not remarkable. The thyroid weighed 40 Gm. and seemed to be slightly enlarged and nodular.

Microscopic examination showed moderate congestion of the sinusoids and central veins of the liver. The adrenal cortex (Fig. 1) appeared atrophied especially in the glomerulosa layer where the cells were decreased in number, and those remaining appeared small with pyknotic nuclei. The thyroid (Fig. 2) acini were lined with high columnar epithelium, and there were only small amounts of colloid in the acini. Some of the fibrous tissue septa between the acini contained large aggregations of densely packed lymphocytes. Striated muscle bundles (Fig. 3) appeared atrophic in many areas with fibrous

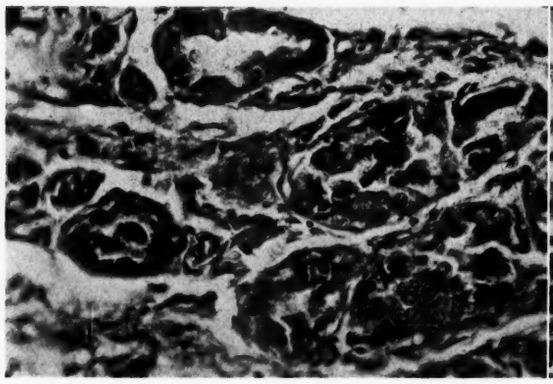

FIG. 1. Patient J. B.; thyroid; hyperplasia of epithelium high columnar cells; marked diminution in colloid content. E M B × 225.

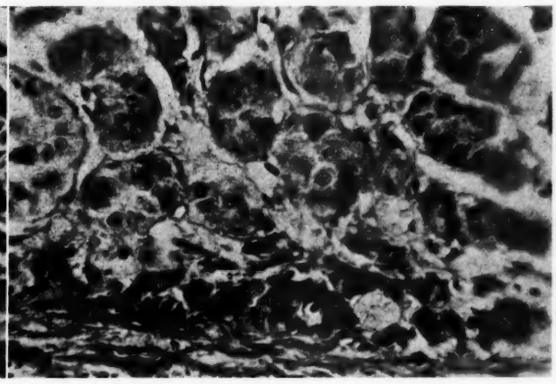

FIG. 2. Patient J. B.; adrenal cortex; atrophy of the zona glomerulosa. Cells are decreased in number and those remaining are small and have pyknotic nuclei. H and E × 450.

replacement of muscle fibers and loss of transverse striations. Occasional areas showed aggregations of lymphocytes. The pituitary was not remarkable.

CASE V. A twenty-two-year-old female with marked weakness of the arms and legs, with atrophy of the muscles of the shoulder girdle, had classical signs and symptoms of thyrotoxicosis. Three weeks after thiobarbital therapy was instituted a four-fold increase in muscular strength had occurred. (Chart 4.)

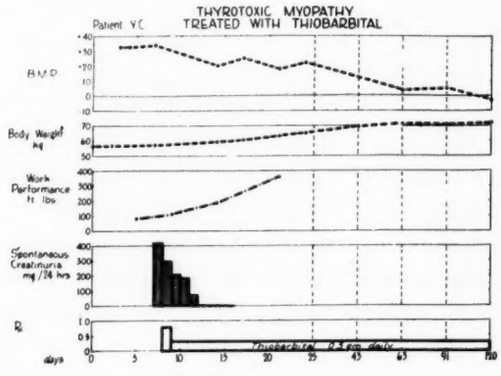

CHART 4.

Y. C., No. M66567, a twenty-two-year-old single housekeeper, entered the Peter Bent Brigham Hospital on June 13, 1944, because of nervousness, weight loss and weakness. She had been in good health until eight months before admission when she had had a severe sore throat and tonsillitis. Following this episode she had felt weak, sweat profusely and lost 10 pounds during the following month. Exophthalmos had then been noted for the first time. Her most prominent symptom had been the marked weakness of her arms and legs. This progressed so that it had become impossible for her to climb stairs, and she had been unable to raise her arms to comb her hair. Six months prior to admission she had been started on iodine, and there had been a temporary remission in all her symptoms. Two and one-half months before entering the hospital she had stopped the iodine medication. Since then she had lost 30 pounds and had become increasingly

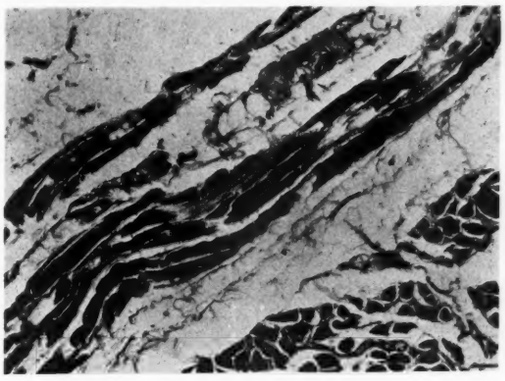

FIG. 3. Patient J. B., skeletal muscle; atrophic muscle bundles with fibrous replacement of muscle fibers. H and E × 225.

more nervous. Sweating had been more marked, and she had noted intolerance to warm weather. There had been considerable muscle weakness especially of the arms and legs with a definite decrease in the size of the muscles. She had had considerable exertional dyspnea and frequent palpitation. Her menstrual periods had always

been regular until two months before admission. At that time she had had an additional period after a seven-day interval.

The patient's past history and family history were non-contributory.

Physical examination on admission showed a well developed and moderately well nourished young woman lying quietly in bed. Her temperature was 98.2°F., pulse 95, respirations 20, blood pressure 140/90 mm. Hg. The skin was warm and moist but of normal texture. There was bilateral exophthalmos, more on the right, with a definite stare, lid lag and convergence defect. Her throat was normal and there was no tremor of the tongue. Her thyroid was considerably enlarged, more so on the right, and there was a definite bruit. Lungs were normal; the heart was not enlarged and sounds were hyperactive. There was a grade III systolic murmur at the left sternal border. No diastolic murmurs were present. The liver edge was just palpable at the costal margin.

There was marked atrophy of the muscles of the shoulder girdle and upper arm, especially the triceps, with marked weakness of the arm especially in extension. There was a fine tremor of the outstretched hands.

Laboratory examination revealed the following: Blood serology was normal. Urine specific gravity was 1.016 with no protein or sugar; spun sediment was clear. Hemoglobin was 14.8 Gm. per cent, hematocrit 38 per cent, and sedimentation rate 14 mm. per hour. White blood count was 6,700 with 70 per cent neutrophils and 23 per cent lymphocytes. Blood urea nitrogen was 5 mg. per cent, total protein 6.5 Gm. per cent, and fasting blood sugar 105 mg. per cent. Stools were negative for occult blood. Venous pressure (method of Burwell) was 115 mm. of water, circulation time (arm to tongue with decholin) was 14 seconds. Urinary 17-ketosteroid excretion was 9.4 mg. per twenty-four hours. On a creatine-free diet her twenty-four-hour urine creatine was 0.42 Gm. Basal metabolic rates before treatment were +33 per cent, +33 per cent and +34 per cent. A chest film showed the heart to be 5 per cent enlarged; there was no substernal thyroid. The work test used consisted in raising a one-pound weight which hung from a rope attached to a pulley at the foot of the bed. Performance was recorded as the number of times patient could raise the weight by flexing her arm at the elbow. After 1 mg. of prostigmine there was no increase in work performance.

On her 7th hospital day the patient was given a large initial dose of thiobarbital 1.0 Gm. and received 0.3 Gm. daily thereafter. (Chart 4.) There was an immediate and striking reduction in spontaneous creatinuria associated with extremely low creatinine excretion on the day following 1.0 gm. of thiobarbital. (Table III.) It seems probable that this was the result of greatly depleted creatine reserve associated with a rapid retention of creatine in a patient maintained on creatine-free diet. Creatinine values subsequently rose as creatine disappeared from the urine. After one week she improved steadily. Her skin became drier. Her basal metabolic rate dropped to between +18 per cent and +22 per cent at discharge. She gained 7.2 kg. in weight. Before treatment her work performance was 60 with the right arm and 100 with the left. She gradually improved in strength so that by discharge she was able to do 330 on the right and 400 on the left.

The patient was discharged on 0.3 Gm. of thiobarbital daily and was seen in the clinic two weeks later. During that period she gained 4.4 kg. Her gland was smaller, and there was no bruit. Six weeks later her basal metabolic rate was +5 per cent. She had gained 2.0 kg. and was feeling well and strong. She was last seen on November 14, 1944. At that time she was taking 0.1 Gm. of thiobarbital daily, and her basal metabolic rate was −3 per cent. Her weight was well maintained. She felt stronger than she had before the onset of her symptoms and was working in a mill doing moderately hard work. She had no tremor of her hands. Her heart was not hyperactive and no murmurs could be heard. Her muscles were of normal size and strength.

ANALYSIS OF CASES

Age and Sex. The cases which we present and those reported by McEachern and Ross[11] are too few to provide reliable statistics on the age and sex incidence of

chronic thyrotoxic myopathy. It is our impression from the data at hand that it occurs in an older age group than does uncomplicated thyrotoxicosis. It also appears that males are frequently affected with a sex ratio different from that reported by Means[1] for uncomplicated thyrotoxicosis in Boston, in which the proportion of males to females is one to four.

Signs and Symptoms. The duration of symptoms in the five patients constituting this report was two to eight months prior to hospitalization. There is no doubt, however, but that symptoms had been present in mild form for a somewhat longer period. In all five patients the presenting complaint was weakness and fatigability. In three, weakness had progressed to such a point that the patients were bedridden and two patients (E. M. and J. B.) were so weak that they were unable to feed themselves.

Weakness of the legs was especially marked. All patients complained of great difficulty in climbing stairs. The most striking muscular atrophy, however, involved the muscles of the shoulder girdle, and in one patient there was winging of the scapula. Involvement of the small muscles of the hands and feet previously noted in patients with chronic thyrotoxic myopathy[11-14] did not occur in these patients although it has been observed in a subsequent case. In none of our patients did we observe the fibrillary twitchings which had been seen in several of the patients described by McEachern and Ross,[11] nor did we note the facial atrophy described by Ayer, Means and Lerman.[12] One patient (E. M.) presented symptoms of bulbar involvement with thick speech and regurgitation of fluids through her nose.

In all the patients one or more of the signs of thyrotoxicosis were present. In one these were minimal, consisting only of tachycardia and a dry, warm skin. Two had moderate enlargement of the thyroid, while in two others this was marked. Three of the patients had classical eye signs. These included stare and lid lag in two and definite exophthalmos in a third. In four of the five patients it was possible to make a presumptive diagnosis of thyrotoxicosis by a careful history and physical examination.

Laboratory Data. We observed no clinical improvement in any of our patients after injection of 1.5 mg. of prostigmine. No myograms were made, however. The absence of prostigmine effect is at variance with earlier observations.[11,15]

In all of our patients there was a significant spontaneous creatinuria ranging from 100 to 590 mg. per twenty-four hours. In all but one patient (G. M.) there was a significant decrease in creatinuria shortly after treatment was instituted. Creatine tolerance tests[16] were done on two patients (G. M. and M. S.), and it was found that there was considerably less creatine retention than normal.

Twenty-four hour urinary 17-ketosteroids[17] were studied in four cases. The two male patients with gonadal atrophy (G. M. and M. S.) had excretions of 8.3 and 8.6 mg. per twenty-four hours respectively, which is a low value when compared to the normal of 12 to 20 mg. for this method. One female patient (E. M.) excreted only 2.7 mg. of 17-ketosteroids per twenty-four hours which is a very low value, whereas another female patient (Y. C.) excreted 9.4 mg. which is normal (9 to 15 mg.). Urinary 17-ketosteroid determinations were not done on patient J. B.

One patient had paroxysmal auricular fibrillation (E. M.), and two had some degree of cardiac enlargement by *x*-ray (E. M. and Y. C.). Two patients (G. M. and E. M.) showed an abnormally rapid circulation time which decreased to normal after treatment.

Clinical Course. One patient (M. S.) was treated surgically after preparation with

iodine and made a good recovery. Six months postoperatively he showed signs of myxedema which were relieved with thyroid U.S.P. 60 mg.

Two patients (G. M. and E. M.) were treated with thiouracil and one (Y. C.) with a related compound, thiobarbital. The response to treatment was dramatic in all instances. All three patients had a reduction in basal metabolic rate and an increase in strength within two weeks after starting treatment. It is interesting to note that marked objective increase in muscular strength occurred before there was an appreciable gain in body weight. One patient (E. M.) who had been bedridden and unable to feed herself was able to be up and around the ward after one week of treatment with thiouracil.

All four of the patients were completely rehabilitated after treatment of the underlying thyrotoxicosis and were able to take up their occupations which they had dropped at the onset of their symptoms.

The two male patients, despite the fact that they were able to resume their work, felt some residual weakness although there was no visible evidence of muscular atrophy. Because of the gonadal atrophy and low urinary 17-ketosteroid excretion, these patients were given 30 mg. daily of methyl testosterone. On this regimen both noted an increase in muscular strength. In one patient injections of testosterone propionate were substituted with the same result as with methyl testosterone orally. At the time of the testosterone treatment neither of these patients was thyrotoxic.[18]

Pathology. One patient (J. B.) with marked atrophy and with little clinical evidence of thyrotoxicosis was admitted to the hospital in a moribund state and died before response to treatment. Pathological examination showed important changes in the thyroid, adrenal, and skeletal muscles. The thyroid (Fig. 1) showed the typical picture of hyperplasia with large irregular cells and absence of colloid in the acini. The adrenal (Fig. 2) showed atrophy of the zona glomerulosa. The skeletal muscle (Fig. 3) showed many of the changes described by Askanazy.[19] There was marked atrophy with fatty infiltration of the muscles, loss of transverse striations, and replacement of muscle fibers by fibrous connective tissue. In some areas infiltration of lymphocytes was present.

The thyroid removed at operation in patient M. S. showed hyperplasia with iodine involution. It weighed 38.5 Gm. Some of the acini were small, devoid of colloid and lined with high columnar epithelium. Others were larger, filled with colloid and lined by flattened epithelium.

MYASTHENIA GRAVIS AND THYROTOXICOSIS

The combination of myasthenia gravis and Graves' disease is rare. To date six cases have been reported.[20-25] This association is of considerable interest, since the myasthenia of chronic thyrotoxic myopathy superficially resembles myasthenia gravis and may easily be confused with it. Secondly, it is important to detect thyrotoxicosis when it occurs in the presence of true myasthenia gravis, since the correction of the underlying thyroid disorder may markedly improve the course of the disease.

Case Reports and Observations. We wish to present another instance of the combined diseases (myasthenia gravis and thyrotoxicosis) and also to present a follow-up on a second case previously described.[25] Data on the clinical courses of the two patients have been summarized in Table II.

CASE VI. A female, aged fifty-nine, had blurred vision, difficulty in accommodation, ptosis of the eyelids and minimal signs of thyrotoxicosis. Treatment with thiobarbital in the absence of prostigmine was followed by a reduction in basal metabolic rate and increase in

TABLE II
MYASTHENIA GRAVIS AND THYROTOXICOSIS

Patient	J. C. Case VI	N. G. Case VII
Sex and age	Female, 59 years	Female, 50 years
Duration of symptoms	Eye changes 6 years; 1 month generalized weakness	9 years myasthenia gravis
Thyroid enlargement	0	+
Eye signs	Ptosis	Ptosis, exophthalmos, ophthalmoplegia
Tremor	0	+
Muscular involvement	Generalized weakness of all muscles; ptosis and diplopia; regurgitation of fluids	Marked generalized weakness, ptosis, diplopia
Fasciculation	0	0
Initial basal metabolic rate—%	+17	+46
Spontaneous creatinuria mg./24 hours	220	420
Creatine tolerance test* % retention of ingested creatine	60	22
Cardiac enlargement	0	+
Prostigmine test	Marked improvement	Marked improvement
Treatment	Iodine followed by thiobarbital and prostigmine	Iodine followed by subtotal thyroidectomy
Result	Definite increase in muscular strength; ptosis disappeared	Four-fold increase of strength and gradual reduction of prostigmine requirement
Basal metabolic rate after treatment—%	−6 (5 months)	+3 (6 years)

* Normal for males 85–100% retention; normal for females 80–95% retention.

TABLE III
URINARY CREATINE AND CREATININE FOLLOWING THE ADMINISTRATION OF THIOBARBITAL
Patient: Y. C.

Date	Dose of Thiobarbital Gm.	Urinary Creatinine Gm.	Urinary Creatine Gm.
6/18–19	0	0.7	0.4
19–20	1.0	0.7	0.3
20–21	0.3	0.5	0.2
21–22	0.3	0.8	0.2
22–23	0.3	0.8	0.1
23–24	0.3	1.1	0.0
24–25	0.3	0.9	0.0
25–26	0.3	0.5	0.0
26–27	0.3	0.7	0.0
27–28	0.3	0.7	0.0

Patient maintained on a low creatine diet (meat free) throughout this study.

muscular strength. Treatment with prostigmine alone prior to above therapy also resulted in improvement. (Chart 5.)

J. C., No. M66069, an Italian housewife, aged fifty-nine, entered the Peter Bent Brigham

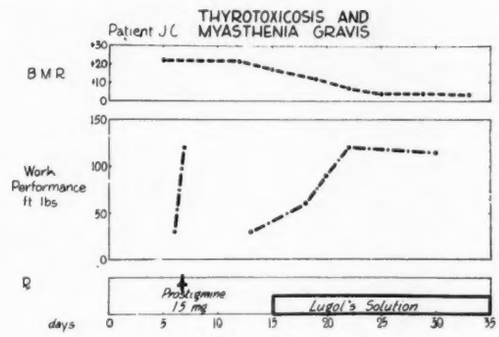

CHART 5.

Hospital on March 20, 1944, complaining of intermittent muscular weakness and pain of two years' duration. She had been well until seven years before admission when she had noted weakness of her left leg on walking. One year later she had begun to have blurred vision with difficulty in accommodating, ptosis of her eyelids and imbalance of her ocular muscles with difficulty in moving her eyes and with diplopia. She had been given prostigmine by her local physician with complete relief of symptoms at first. She had taken the medication sporadically and had been moderately well until three years before admission when she had developed "tolerance" to the drug. Ptosis had continued as a predominant symptom with little oculomotor difficulty. She had had marked weakness and easy fatigability. One month before admission there had been a marked exacerbation of her symptoms. She had developed extreme ptosis. Her legs had become so weak that she had not been able to climb stairs, and finally she had to go to bed. Two weeks before admission she had had difficulty in swallowing for the first time.

There was no past history of intolerance to warm weather, sweating, nervousness or tremor. Family history was non-contributory. Physical examination on admission showed a well nourished, middle-aged woman lying in bed. Movement was difficult and occasioned considerable pain in her muscles. Her temperature was 99°F., pulse 120, respirations 28, blood pressure 160/100 mm. Hg. She spoke clearly. There was no significant lymphadenopathy. There were marked hypertrophic changes in the terminal phalanges of the fingers. Both eyelids showed marked ptosis, more on the left. Extra-ocular movements were weak and un-

FIG. 4. Patient J. C. prior to treatment.

FIG. 5. Patient J. C. twenty-five minutes after administration of 1.5 mg. of prostigmine subcutaneously.

coordinated with inability to look upward with both eyes and weakness of lateral movement on the left. Pupils reacted normally. Fundi appeared normal and the throat was also normal. There was no apparent difficulty in swallowing. Her thyroid was not enlarged, lungs were normal, the heart was not enlarged, sounds were not hyperactive and rhythm was regular and rapid. There was a grade I systolic murmur at the base. The abdomen was normal.

There was weakness of all muscle groups but no atrophy. There were no fibrillary twitchings or tremor. Reflexes were hypoactive but equal on both sides.

Laboratory examination revealed the following: Blood serology showed nothing abnormal. Urine showed a specific gravity of 1.012 with no protein and a trace of sugar on admission. Spun sediment contained no red cells, 0–3 white cells, and no casts. Hemoglobin was 14 Gm. per cent, hematocrit 42 per cent, white cell count 5,700 with 69 per cent neutrophils, blood urea nitrogen was 15 mg. per cent, total protein 5.9 Gm., fasting blood sugar 107 mg. per cent, cholesterol 272 mg. per cent, calcium 5.0 m.Eq. per liter, and phosphorus 1.9 m.Eq. per liter. The stool was normal. Initial basal metabolic rates were +17 per cent and +12 per cent. She excreted 0.59 Gm. of creatinine and 0.22 Gm. of creatine per twenty-four hours. Creatine tolerance test showed retention of 85 per cent of the test dose. *X*-ray film of the chest showed some coarsening of the lung markings. The heart was transverse in position but not enlarged. Films of the skull showed mild hyperostosis frontalis interna. An electrocardiogram was normal except for the presence of Q_3. The intravenous glucose tolerance test showed a rise to 365 mg. per cent with a return to normal in two and one-half hours.

Diagnosis of myasthenia gravis (Chart 5) was definitely established by striking improvement with prostigmine therapy and by the marked exacerbation of signs and symptoms after quinine therapy. (Figs. 4, 5 and 6.) Because of persistent tachycardia, warm, moist skin, slight elevation of the basal metabolic rate and the spontaneous creatinuria, thyrotoxicosis was suspected. She was given iodine with a resultant drop in basal metabolic rate from +22 per cent, +22 per cent, and +17 per cent before treatment to +12 per cent in five days, +7 per

cent in eight days and thereafter +4 per cent. Basal pulses dropped from between 80–90 to 70–80. Her muscle strength (without prostigmine) improved considerably; before starting the iodine therapy she was able to raise a 6-pound weight only ten times; nine days after taking iodine she was able to raise it twenty times. Spontaneous creatinuria dropped to 0.10–0.04 Gm. per twenty-four hours sixteen days after starting the iodine. These facts plus the marked improvement in well-being indicated hyperthyroidism. Consequently she was started on thiobarbital 0.1 Gm. daily. In addition she was given prostigmine which caused a more marked increase in muscular strength. She was discharged on 120 mg. of prostigmine bromide by mouth and thiobarbital 0.1 Gm.

When seen one month later she was definitely improved. She was less weak and was able to climb stairs and to comb her hair, which she could not do before coming to the hospital. She had no ptosis or diplopia. Basal metabolic rate was +9 per cent.

Five months later she did not appear to be doing well; her appetite was poor and she had lost 15 pounds. On 150 mg. of prostigmine daily she had no ptosis but could climb stairs only with difficulty. She complained of being cold most of the time, and her skin was dry and cool. Basal metabolic rate was −6 per cent. Prostigmine was raised to 180 mg. daily, and thiobarbital was stopped.

The patient was last seen August, 1945. At that time she was considerably stronger and able to get around without difficulty, and she had reduced her daily intake of prostigmine to 90 mg. from the earlier requirement of 180 mg. daily. The thyroid gland was firm and twice normal size. There was no evidence of thyrotoxicosis, her basal metabolic rate being −8 per cent.

CASE VII. A female, fifty years of age, received prostigmine therapy for myasthenia gravis over a period of nine years with considerable benefit. During this period thyrotoxicosis was suspected but never proved. Following the administration of iodine, there was a reduction in basal metabolic rate and creatinuria. Following subtotal thyroidectomy a striking improvement in muscular strength occurred, and a great decrease in prostigmine requirement was noted.

FIG. 6. Patient J. C. following the administration of quinine sulfate (1.2 Gm. total dose) given over a period of ten hours.

N. G.,* No. M145931, a negro school teacher, fifty years of age, was first seen at the Johns Hopkins Hospital on February 5, 1929, complaining of double vision and drooping of the eyelids for the previous three months.

Physical examination showed a poorly nourished colored woman with tachycardia and moist skin. There was marked ptosis of both eyelids, left external strabismus and bilateral exophthalmos. The thyroid was not enlarged, but an audible bruit was present. The heart was enlarged, and there was an apical presystolic rumble. Skeletal muscles contracted strongly at first but fatigued easily. Blood, urine and spinal fluid were normal. Basal metabolic rate ranged between +10 per cent and +36 per cent. During subsequent admissions she complained of increasing weakness of the extremities and trunk with difficult breathing. In November, 1930, she received *x*-ray treatment over the thyroid gland with some improvement in strength. In September, 1937, she was started on prostigmine, and there was considerable improvement. Treatment could not be continued, however,

* This case was previously reported by Thorn and Tierney.[55]

because of diarrhea and increased menstrual flow. In July, 1938, she was seen again because of an exacerbation of her symptoms. At this time she had a five-week history of increased nervousness, tremor of her hands, sweating, palpitation and weight loss despite increased appetite. She had marked weakness of her arms and legs so that she was unable to walk without assistance. Physical examination showed, in addition to the findings previously noted, increased nervousness, exophthalmos, bilateral ptosis and ophthalmoplegia. The thyroid was enlarged. There was marked weakness of her skeletal muscles and a coarse tremor. Her basal metabolic rate was +46 per cent. Serum cholesterol was 192 mg. On a creatine-free diet the spontaneous urinary creatine excretion was .420 Gm. per day. In the creatine tolerance test she retained 22 per cent of the test dose. After these preliminary studies she was given Lugol's solution. Her creatine excretion fell to .050 Gm. per day, and 59 per cent of the oral dose of 2.61 Gm. of creatine was retained as compared to 22 per cent before iodine therapy. Her basal metabolic rate decreased slightly during this period. After twenty-five days of iodine treatment a subtotal thyroidectomy was performed. Postoperatively there was general improvement in strength, and she was soon able to walk even in the absence of prostigmine therapy, but the ptosis and ophthalmoplegia did not change appreciably. With prostigmine treatment after operation the ptosis disappeared completely, and she had sufficient strength to return to work.

In the six and one-half years since operation her prostigmine requirement has steadily dropped so that at the present time she takes less than 15 mg. per day to maintain her strength. During this period she has been able to continue her work as a school teacher, although there is still residual weakness of her face and skeletal muscles on sustained effort.

Analysis of Cases. The two patients (J. C. and N. G.) with myasthenia gravis who developed thyrotoxicosis were females, aged fifty-nine and fifty years, respectively. One had had symptoms of myasthenia gravis for six years and symptoms of hyperthyroidism for one month. The other had been followed for nine years before a diagnosis of thyrotoxicosis was definitely established. Both were typical cases of myasthenia gravis with ptosis, oculomotor weakness and moderate generalized weakness. Both responded to prostigmine. In one patient signs of thyrotoxicosis were minimal and consisted only of slight thyroid enlargement, tachycardia and warm moist skin. The other patient had an enlarged gland, with exophthalmos and tremor of hands. Neither patient showed striking muscular atrophy, and weakness was of the myasthenia gravis type, i.e., it became more marked on sustained effort. There were no fibrillary twitchings. Both patients had elevated basal metabolic rates of +17 and +46 per cent, respectively. Both had spontaneous creatinuria of 220 and 420 mg. per twenty-four hours, respectively. Both showed abnormally high creatine excretions following the administration of creatine. On test doses of iodine there was a definite increase in strength of muscles, and there was a drop in the spontaneous creatinuria which does not occur in uncomplicated myasthenia gravis treated with iodine.[25] One patient was treated with thiobarbital and the other had a subtotal thyroidectomy performed. In both there was a gradual increase in muscular strength. The prostigmine requirement in the one patient followed for six and one-half years gradually declined so that at the end of that period she was taking occasional doses of 15 mg. per day.

COMMENTS

In these patients with striking myopathic changes in thyrotoxicosis it is of interest to speculate on what particular factors or mechanisms conditioned the response of these individuals in such a way that the myopathic changes predominated in the manifestations of thyrotoxicosis.

In our two patients with myasthenia gravis the primary disease was markedly aggravated by thyrotoxicosis. This has also been reported in periodic paralysis.[6] It has been suggested that an occult primary myopathy underlies many cases of thyrotoxic myopathy. If this were the case, one might expect some evidence of the primary neuromuscular disease to persist following correction of the complicating thyrotoxicosis, but this has not been observed in our five patients.

There is some evidence that an associated disturbance of steroid hormone production occurs in these patients, as indicated by (1) low urinary excretion of 17-ketosteroids in several patients, (2) testicular atrophy in the two males, and (3) the degenerative changes in the adrenal demonstrated in patient J. B. It has been found experimentally that normal rats, when injected with 1 mg. of thyroxin daily for fifteen days, exhibit striking increase in adrenal and testicular weight despite generalized weight loss and wasting.[26] This suggests that the steroid hormone requirement may be increased in thyrotoxicosis. That a deficiency of these hormones conditions an over-all unfavorable response in thyrotoxicosis is suggested by the following:

1. Adrenalectomized and/or castrate animals treated with thyroxin have a much higher mortality rate than normal animals treated with the same dose of thyroxin.[26]

2. Administration of adrenal cortical and gonadal hormones increases the survival rate of normal adrenalectomized and castrate animals given thyroxin.[26]

3. It is well known clinically that patients with adrenal insufficiency, both primary and secondary, tolerate thyroid administration very poorly.[1,27]

These factors most certainly have a marked direct effect on muscle. Hertz et al.[28] have shown clearly that testosterone propionate has a marked nitrogen retaining effect even in the presence of thyrotoxicosis. That adrenal cortical hormone has a direct effect on the metabolism of muscle tissue has been clearly shown in the hexokinase studies of Cori et al.[29] The hypothesis that the combination of thyrotoxicosis and steroid hormone deficiency can cause marked myopathy certainly appears reasonable.

Creatinuria and a decrease in the creatine and phosphocreatine content of the muscle are common findings in thyrotoxicosis.[30] The fact that phosphocreatine is an intermediate in the cycle of energy release in the muscle strongly suggests that the clue to the mechanism of thyrotoxic myopathy may be found in careful study of creatine metabolism in these patients. Many of the steps in the synthesis and utilization of creatine have been elucidated in recent years by a combination of experiments on intact animals and tissue slices and with isotopes of nitrogen and hydrogen. Glycocyamine, the unmethylated creatine, is formed in the kidney by the transfer of the amidine group from arginine to glycine. (Fig. 7.)[31] This synthesis can be increased by feeding glycine or arginine.[32] The glycocyamine formed is methylated in the liver by transfer of a methyl group from the methyl pool (chiefly choline) by way of methionine. (Fig. 8.)[33] In the muscle the creatine is phosphorylated to phosphocreatine (Fig. 9)[24] which in turn replenishes the phosphate groups of adenyl phosphate to form adenosine triphosphate, the breakdown of which has the closest known energy linkage with the actual shortening process of the muscle fiber. In this step creatine phosphate appears to form creatinine, which is eliminated from the body in the urine at the rate of about 2 per cent of the total body creatine per day.[31]

In thyrotoxicosis there are three possible mechanisms for the creatinuria:

(1) *Increased Synthesis of Creatine in the Body.* In two patients with uncomplicated thyro-

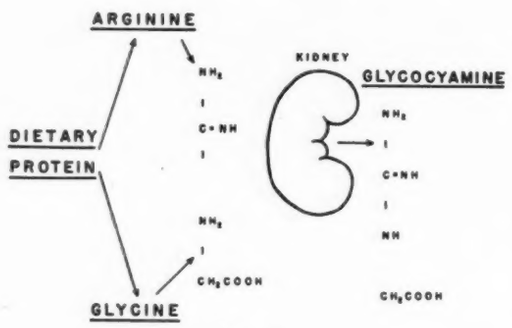

FIG. 7.

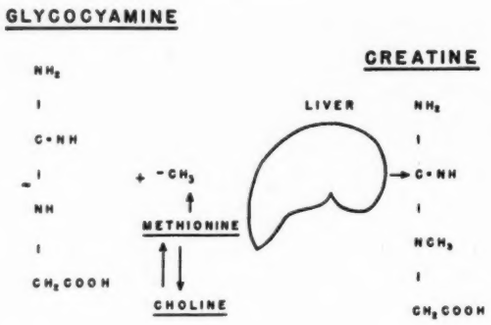

FIG. 8.

toxicosis twenty-four-hour glycocyamine excretion was measured and this was not increased. Although methylation can proceed at a rapid rate, it has been shown that where there is increased synthesis of creatine, as in treatment with methyl testosterone, there is increased glycocyamine excretion.[35]

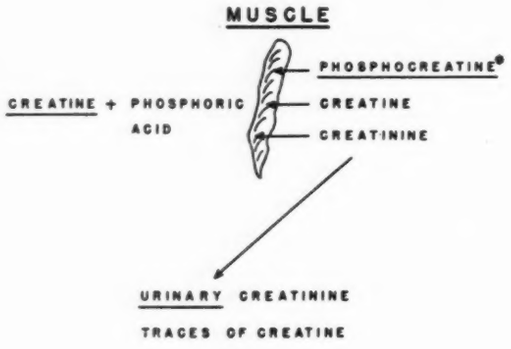

FIG. 9.

(2) *Direct Loss of Creatine from the Muscle.* There is no doubt that this is an important source of urinary creatine. In a rat given thyroxin at the rate of 2 mg. per day the loss of creatine in the urine divided by the weight loss showed a creatine concentration of the order of magnitude of muscle.[26] In chronic thyrotoxicosis, however, the muscle stores of creatine alone are probably not sufficient to account for the prolonged creatinuria.

(3) *Failure of Storage and Utilization of Creatine in the Muscle.* That this is a factor in operation in thyrotoxicosis is clearly demonstrated by the decreased creatine tolerance test and by the clinical studies of Wilkins and Fleischmann.[36] A high percentage of a dose of creatine which can be stored easily by a normal person is excreted in the urine of most patients with thyrotoxicosis.[37] Since it appears that creatinine is formed from phosphocreatine, the decreased creatininuria so often associated with creatinuria suggests that this failure in storage may result from a failure of phosphocreatine synthesis. In short, the creatinuria of thyrotoxicosis may represent a combination of increased muscle breakdown which is non-specific and parallels the negative nitrogen balance, and a specific failure in creatine utilization and storage.

There appears to be little correlation between the severity of the myopathy and the extent of creatinuria. (Table 1.) In the four patients studied the spontaneous urinary creatine ranged between 100 and 590 mg. per day. There did appear to be a much greater spontaneous creatinuria in the two female patients than in the two male patients. (Table 1.)

It does not appear that chronic thyrotoxic myopathy can be explained on the basis of a simple exaggeration of the usual creatine metabolic defect in thyrotoxicosis, since there is no striking increase in creatine excretion in these patients over that seen in uncomplicated thyrotoxicosis. It is suggested that the defect may be one rather in the direction of failure to maintain adequate synthesis to meet the abnormal demands. This point requires further investigation.

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Disturbance in Salt and Water Metabolism in Hypertension*

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Evidence that the adrenal cortex may be concerned in the development or maintenance of essential hypertension in man has previously been reported.[1,2] It is of interest that drastic reduction in sodium intake may result in a decline in blood pressure in hypertensive patients,[3] possibly through the established influence of the adrenal cortex on salt and water metabolism.

In the course of clinical studies aimed at extending observations on the rôle of sodium in hypertensive vascular disease, it was noted that patients with hypertension differed from control subjects in their response to sodium restriction. It is the purpose of this study to report these findings.

EXPERIMENTAL

All studies were carried out on the wards of the Presbyterian Hospital. Patients with uncomplicated hypertensive vascular disease were included only if the arterial pressure consistently exceeded 140/90 mm. of mercury and in the absence of cardiac pain or insufficiency, renal or cerebral complications or fever. All patients were free of albuminuria, showed normal phenolsulfonephthalein excretion and urine concentration tests, and in all instances the venous pressure was within normal limits. Control subjects included afebrile convalescent patients and healthy volunteers under hospital observation without evidence of cardiac, renal or endocrine disease and with repeatedly normal blood pressure readings.

Both groups were comparable in sex distribution and included as wide an age span as possible. To eliminate any cyclic changes in fluid balance, experiments on female subjects were carried out one to two weeks after the last menstrual period. Thin and obese patients were included in both series studied. All subjects were weighed daily on the same scales before breakfast and before bowel movement.

Sodium chloride was administered by mouth using weighed salt shakers, additional supplements being given in some instances in the form of enteric-coated tablets. Identical salt-poor daily menus were prepared. Repeated direct analyses of aliquots taken from an entire day's cooked diet gave values of between 0.25 to 0.35 Gm. of sodium or considerably less than 1 Gm. of sodium chloride per day. It was found that such diets were not difficult to prepare, permitting the inclusion of sweet butter, salt-free bread, two daily servings of meat and small portions of cream, as well as sugar, fruits and vegetables. These salt-poor diets yielded 1,700 to 2,200 calories and 70 to 80 Gm. of protein, and did not include special ingredients such as dialyzed milk.

Under different conditions of activity and environmental temperature, and with different amounts (4 to 10 Gm.) of added sodium chloride, twelve control and twelve hypertensive subjects were placed on constant food and fluid intake. Paired observations, using one control and one patient

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TABLE I

RESULTS OF SODIUM RESTRICTION IN CONTROLS AND HYPERTENSIVES

	No.	Age	Sex	Ambulation before and during Study	Antecedent NaCl Intake	Weight					Before and after 24 hrs. Sodium Restriction						
						Day 1	2	3*	4	5	Weight Change	Hematocrit Change	Total Serum Protein Change	CO_2 Content	Serum Chlorides As NaCl	Urine Volume Change	Urine Chlorides
					Gm.	(Kilos)					Kilos	% Cells	Gms./ 100 cc.	(Milliequiv./Liter)		cc.	Meq/24 Hr., as NaCl.
Normal Subjects	1	48	M	quiet ambul.	5	76.38	76.66	*76.42*	*75.38*		−1.04						
	2	15	F	bed	5	74.70	74.72	*74.73*	*74.10*	74.70	−0.63	+1	0	25.5–26.0	102.8–101.2	+370	130–96
	3	34	M	average amb.	10	73.06	73.10	*73.18*	*71.58*	72.86	−1.60	+1	+0.3		103.1–102.2	+650	154–96
	4	23	F	" "	7	70.14	70.00	*70.03*	*68.84*	69.72	−1.19	+1	+0.1	27.6–28.0	98.9– 96.3	+475	
	5	33	F	" "	5	57.14	57.04	*56.86*	*55.54*	56.63	−1.32				100.7–100.8	+620	123–62
	6	34	M	quiet ambul.	6	72.10	72.08	*72.00*	*71.21*	72.04	−0.69					+645	
	7	55	M	" "	5	59.69	59.96	*60.55*	*58.70*	60.07	−1.85					+960	
	8	87	F	bed	5	47.43	47.65	*47.87*	*47.32*	47.43	−0.55					+300	
	9	51	M	quiet ambul.	4	63.00	62.70	*62.70*	*62.75*	63.25	−0.55	−1	−0.3	27.7–28.4	96.5– 97.2	+250	77–49
	10	48	F	average amb.	8	65.63	65.76	*65.93*	*64.92*		−1.01					+500	
	11	20	F	quiet ambul.	5	49.74	49.24	*49.35*	*48.66*	49.31	−0.69	+2	+0.2	27.5–26.6	100.1– 97.5	+220	
	12	45	F	" "	5	69.16	69.28	*69.51*	*68.51*	68.90	−1.00						
						mean = −1.01											
Hypertensives	1	44	F	average amb.	7	62.12	62.42	*62.70*	*62.22*		−0.48	−2	−0.2	24.2–24.4	104.8–105.2	+300	51–52
	2	45	M	quiet ambul.	7	59.17	58.91	*58.85*	*58.84*	58.56	−0.01	+1	+0.1	27.8–27.8	105.6– 99.5	+100	111–61
	3	22	M	bed	8	50.11	50.10	*50.05*	*50.10*		+0.05	+1	+0.1	26.1–27.9	98.0– 95.2	− 75	
	4	44	F	quiet ambul.	6	68.52	68.48	*68.36*	*68.15*		−0.21		+0.1		104.3–103.3	+100	80–38
	5	44	F	" "	9	65.00	64.75	*64.85*	*64.53*	64.40	−0.32			29.3–28.9	103.2–101.3	+400	148–46
	6	45	M	average amb.	5	60.50	60.66	*60.60*	*60.13*	60.34	−0.47	−1	−0.2	28.1–28.4	101.8–100.0	−160	
	7	55	F	quiet ambul.	8	51.77	51.93	*51.61*	*51.43*		−0.18	0	+0.2	27.1–27.5	100.7– 99.6	+160	71–56
	8	46	M	average amb.	7	58.61	58.30	*58.36*	*58.31*	58.19	−0.04						83–45
	9	46	F	bed	5	50.64	50.50	*50.24*	*50.40*		+0.14					−275	
	10	61	F	quiet ambul.	5	50.70	50.95	*51.25*	*50.80*		−0.45						
	11	63	F	average amb.	5	62.70	62.76	*62.86*	*62.69*	62.80	−0.17					+ 75	
	12	36	F	quiet ambul.	4	58.00	57.85	*57.90*	*57.67*	57.75	−0.23	−1	+0.3	26.6–27.3	101.5– 99.5	+200	77–45
						mean = −0.198											

* Start of 24 hr. sodium restriction.

with hypertension, were made whenever possible. After two days on a constant regimen, the added sodium chloride was withdrawn for twenty-four hours (beginning with breakfast on the third day), but without other change in activity, diet or fluid intake. Sodium chloride administration was resumed on the morning of the fourth day.

RESULTS

In association with rigid sodium restriction for twenty-four hours, a conspicuous weight loss occurred in all of the control non-hypertensive group which was not apparent in any of the hypertensive subjects (Table I, Fig. 1.) After one day without added salt, the mean weight loss of the control group was 1.0 kg. as compared to 0.2 kg. in the patients with hypertension. Calculation of the standard error of the differences proved these values to be statistically significant. No matter whether a control subject lay in bed with little clothing on a cool day (mean temperature 59°F.), or a warmly clothed hypertensive patient exercised vigorously on a hot day (mean temperature 81°F.), all of the control subjects lost more than 0.55 kg., whereas weight loss among the hypertensive series never exceeded 0.48 kg.

In addition, the control group exhibited a diuresis after salt withdrawal, whereas the hypertensives showed much smaller varia-

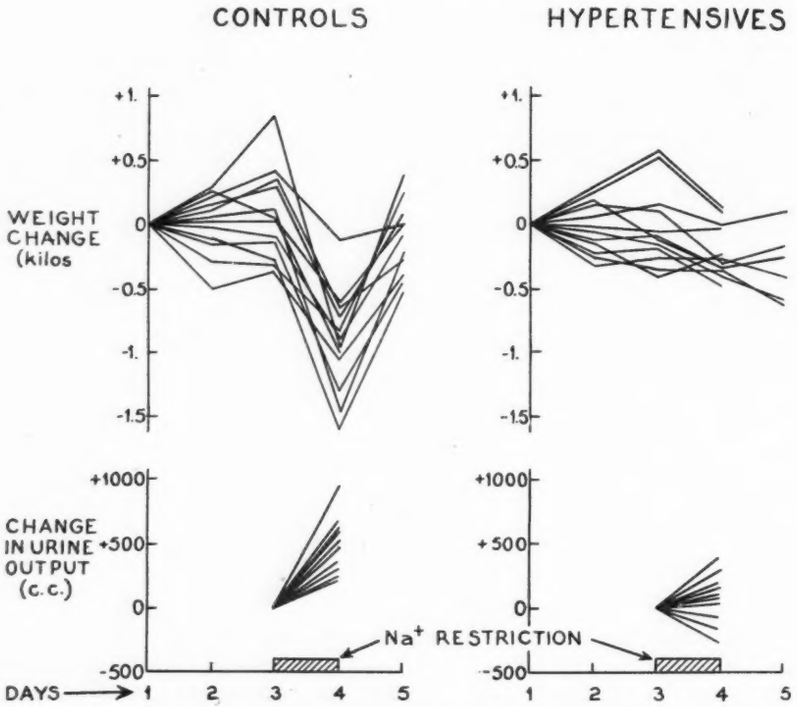

FIG. 1. The effect of salt restriction on weight and urine output in control and hypertensive subjects.

tions in urine output. Furthermore, several in the control group noted increased sweating, insomnia or slight weakness toward the end of the twenty-four-hour period of sodium restriction, none of which symptoms were noted by patients with an elevated blood pressure. Two control subjects, who were later placed on salt restriction for forty-eight hours and developed the above symptoms to a greater extent on the second day, also complained of subjective disturbances similar to those described by McCance in salt-depleted normal individuals.[4] On the other hand, it was shown repeatedly that hypertensive patients could tolerate weeks of the low sodium diet without discomfort of any kind.

Urine sodium determinations were made on twenty-four-hour samples in two control subjects and in two hypertensives, before and after salt restriction was instituted, on the same day in both pairs, and after identical menus and sodium intake. Following the withdrawal of salt, the sodium values in the urine decreased to the same extent in both instances.

Urine chlorides usually decreased in control and hypertensive subjects. Significant changes in hematocrit, total proteins, serum CO_2 and chloride determinations were not observed. Blood pressure levels were not materially affected by the twenty-four-hour period of salt withdrawal.

Calculation of sodium and chloride clearances (UV/P) in two control subjects and two hypertensive patients showed little change in the non-hypertensive individuals following salt restriction but a definite reduction in clearance values in the patients with elevated blood pressure.

COMMENTS

It has been shown that non-hypertensive subjects respond differently to the rigid withdrawal of sodium from the diet as compared with a group of patients with uncomplicated hypertensive vascular disease. Regardless of the amount of activity

or of the antecedent salt consumption, a drastic reduction of sodium intake in control subjects was followed by an immediate and significant loss in weight attributable in part to an associated diuresis. If this was carried much beyond a twenty-four-hour period, a regular pattern of symptoms appeared. Patients with essential hypertension, on the other hand, showed minimal weight change, failed to exhibit a diuresis and were symptom-free.

The decrease in weight in the control group was not entirely explained by the alteration in urine output. As several subjects noted increased perspiration, it is possible that changes in sweat production may have been responsible in part. Preliminary observations suggest that the urine sodium and chloride values were largely influenced by the reduction in sodium and chloride by mouth, rather than by the changes in urine volume, but the net result was a decrease in sodium and chloride clearances in two hypertensive patients studied as compared to minimal change in normal subjects. Whether or not a shift of sodium into cells accompanied the diuresis observed in control subjects remains to be seen.

The mechanism involved in this difference in behavior remains obscure. It is conceivable that the defect is purely renal in origin, secondary to changes produced by hypertension. However, with the exception of the nephrotic syndrome, in which reabsorption is augmented, most kidney disorders involving the tubular elements are associated with a decreased capacity for reabsorption. The effects of a low sodium diet on glomerular filtration and tubular function must be further elucidated.

The inability of hypertensive patients to lose weight and fluids in response to sodium restriction is consistent with the view that the adrenal cortex may be implicated, since the tubular reabsorption of salt and water is known to be influenced by desoxycorticosterone. Furthermore, it has been repeatedly demonstrated that the arterial blood pressure may rise in normal subjects[1] and may exceed normal limits in a considerable number of patients with Addison's disease in the course of treatment with desoxycorticosterone esters.[6-11] Not only has it been suggested that the abnormal liberation of certain adrenal cortical steroids may be concerned in the etiology of hypertension,[2] but recent studies have shown that sodium chloride appears essential for pressor and certain other activities of desoxycorticosterone when administered to rats rendered nephritic with nephrotoxic serum.[5]

CONCLUSIONS*

1. Observations have been made on twelve control subjects and twelve patients with uncomplicated hypertensive vascular disease following the rigid withdrawal of sodium chloride for twenty-four hours.

2. Despite an otherwise constant regimen, sodium restriction was followed by significant weight loss and increased urine output in control subjects which was not evident in hypertensive patients, regardless of variations in environmental temperature and physical activity.

3. A disturbance in salt and water metabolism exists in hypertensive vascular disease as judged by the abnormal response to the abrupt and rigid restriction of sodium in the diet.

4. It is suggested that this difference in response may be referable to primary renal changes or, more likely, to changes in the kidney mediated by the adrenal cortex.

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Thiouracil in Angina Pectoris*

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ALTHOUGH the value of total thyroidectomy for severe angina pectoris has been generally recognized, the procedure has fallen into disuse because of the initial risk, subsequent complications and likely myxedema. Accordingly, when the anti-thyroid agent, thiouracil, was introduced, one of the earliest suggestions for its use in other than thyrotoxic states was as a substitute for thyroidectomy in the control of angina pectoris. Here it was expected that a reversible, risk-free chemical thyroidectomy might be performed with results at least comparable to those formerly attained surgically. That this appears to be a valid assumption is attested to by the report of Raab,[1] in which seven of ten patients with angina responded favorably, and that of Ben-Asher,[2] with eight patients successfully treated.

To determine whether thiouracil is consistently active in this respect, its ability to depress a normally functioning thyroid gland and to lower the basal metabolism must be established. Then, too, toxic reactions from the drug must be infrequent enough not to eliminate too many patients from treatment over an extended period of time. Finally, in this preponderantly subjective disease, a thoroughly objective, skeptical attitude must be adopted by the investigator in evaluating reported changes in the patient's condition.

While there is ample evidence of the thyroid depressant effect of thiouracil in normal animals and in humans with thyrotoxicosis, little data are available demonstrating a similar action on the normal human thyroid. In the thyrotoxic state positive action becomes manifest in an average six to eight weeks, but in the normal it is reasonable to expect a longer time to elapse if the tightly organized pituitary-thyroid relationship is to be disrupted. Astwood has observed the development of myxedema in normal humans after at least five months' continuous administration of the drug. Similar observations have not been reported by any one else, so that this basic question will be answered only as experience accumulates.

Toxic reactions from thiouracil have an unpredictable incidence of 10 to 15 per cent. These consist mainly of drug fever, skin eruptions, leukopenia and agranulocytosis, and their occurrence appears unrelated to dosage or duration of therapy. However, the risk is not too great if a close watch is kept through repeated blood counts, and the patient is instructed to report promptly any untoward development. Except in the case of the skin reactions or leukopenia, when the drug may be restarted at a lower dosage level without recurrent reaction, drug fever and agranulocytosis eliminate the patient from further treatment.

It is quite obvious that in angina, in which so much of the disturbance is subjective, care must be exercised in evaluating reports of improvement which may be wishfully inspired. Interruption of treatment at intervals, with substitution of placebos, is perhaps the best method of testing the validity

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Thiouracil and propyl-thiouracil were supplied through the courtesy of Dr. Stanton M. Hardy, Lederle Laboratories, Inc., Pearl River, New York.

of the improvement, though this may invite toxic drug reactions. Oxygen deprivation tests could be carried out periodically but, as between the two methods, the former appears the more practical. Spontaneous improvement must also be thought of in evaluating the results of therapy but there is no way of tagging this factor so that it must stand as a negative quantity in any final summation of results. One final point worth remembering is that the patient with severe angina, for whom a trial of thiouracil may be especially indicated, will not long maintain his enthusiasm for any method of treatment if genuine relief is not obtained.

With these guiding views, studies were made on a group of eight patients with angina, five of whom were observed for a period of approximately one year. In two the disturbance was mild, in two it was moderately severe and in the remaining four severe. On beginning treatment the action of the drug with its possible ill effects was fully explained and the patients instructed to report promptly any ill effects. Basal metabolic rate determinations and blood counts were at first repeated every two weeks and later every four weeks. The initial dose of thiouracil was either 0.4 or 0.6 Gm. daily, divided into two or three equal doses. This was reduced to 0.3 or 0.2 Gm. daily as soon as there was any improvement. Patients were permitted to continue taking nitroglycerin as necessary and were also allowed to use a mild sedative when unable to sleep.

CASE REPORTS

CASE I. S. G., a fifty-two-year old white male, had had attacks of chest tightness and pain radiating down the left arm for almost a year. He was able to continue work as a tailor as long as he took from four to six tablets of nitroglycerin daily. During the month previous to his first visit, however, the attacks of pain became more frequent and severe and were no longer adequately controlled by nitroglycerin. His activity was greatly limited and he remained closely confined to his home.

His physical examination revealed no distinctive abnormalities. The blood pressure was 150/90, the heart size was normal and there were no murmurs. The EKG showed left axis deviation, small Q_2, flattened T_2 and inverted T_3, and the precordial leads were normal. The initial basal metabolism was minus 15 per cent on March 21, 1945.

Thiouracil, .2 Gm. three times daily, was started and the patient advised to continue using nitroglycerin as necessary. Little improvement was noted during the following three months. The basal metabolism readings during this period were minus 11, 6, 18 and 12 per cent. The patient failed to return for further observation.

Comment. In this instance of severe angina, thiouracil administered continuously for three months in a dosage of 0.6 Gm. daily failed to produce any improvement. The lowest basal metabolism level attained was minus 18 per cent.

CASE II. M. A., a fifty-nine-year old white female, developed chest pain and tightness with shortness of breath on exertion ten months previous to her visit in April, 1944. Hypertension had been present for several years. She was somewhat obese, the blood pressure was 168/90 and there was a grade 2 retinopathy. The thyroid showed bilateral nodular enlargement without evidence of toxicity. The heart sounds were forceful but there were no murmurs. She failed to improve during the next ten months in spite of loss of eighteen pounds and the use of aminophyllin and sedation.

In March, 1945, the basal metabolic rate was plus 1 per cent, the blood cholesterol 245 mg. per cent, and the chest *x*-ray showed no increase in heart size. The EKG showed left axis deviation, small Q_1 and negative T_3.

Thiouracil, 0.2 Gm. three times daily, was started and continued for six weeks without improvement when the patient failed to return for further treatment. The basal metabolism readings during this interval were plus 3, minus 2 and 0 per cent.

Comment. This patient with mild angina failed to improve after six weeks' continuous administration of thiouracil at the rate of 0.6 Gm. daily. The lowest basal metabolism attained was minus 2 per cent.

Case III. B. W., a forty-six-year old white male, noted increasing shortness of breath, tightness of the chest with numbness in both arms, and exhaustion following almost any form of exertion during the two years preceding his first visit.

Physical examination was negative, the blood pressure 140/90 and no heart murmurs were heard. *X*-ray study of the chest showed the heart size at the upper limits of normal. The EKG showed left axis deviation with slurring and notching of QRS and Q_1, Q_3 and QCF_5 present.

A regimen of lessened activity, small meals, no tobacco and aminophyllin and sedatives was followed for four months without improvement. In August, 1945, thiouracil, .2 Gm. twice daily, was started, the initial basal metabolic rate being minus 6 per cent. Subsequent determinations at monthly intervals were plus 2, minus 8, 16, 24, 15, 10, 16, 0, 9, 20 and 8 per cent. Improvement was reported at the end of four weeks and the tightness in the chest disappeared after eight weeks. At this point the thiouracil was reduced to .1 Gm. three times daily.

At the end of four months' treatment the basal metabolic rate was minus 24 per cent and the patient's face was puffed, he was sluggish and complained of sensitivity to cold. The blood cholesterol was 324 mg. per cent. The chest tightness and numbness in the arms had returned but this gradually disappeared during the next two weeks on a reduced dose of .1 Gm. thiouracil twice daily. Treatment was continued for another four months, then terminated. The patient had been entirely symptom-free during this latter period as well as during the subsequent four months' interval without medication. No change was found in the EKG or chest *x*-ray at this time.

Comment. This patient with moderately severe angina, starting with an initial basal metabolism of minus 6 per cent, showed improvement at the end of eight weeks on 0.4 Gm. thiouracil daily. After four months' treatment the basal metabolic rate dropped to minus 24 per cent and myxedema developed. Symptoms returned at this time but disappeared promptly on a lowered dosage of 0.2 Gm. thiouracil daily which was continued for four months. He has remained symptom-free during the subsequent four months without medication.

Case IV. M. C., a fifty-two-year old white male, had recovered from an acute anterior myocardial infarction in 1941 which had been preceded by several months of precordial tightness brought on by exertion, emotional disturbance and exposure to cold. He remained symptom-free until January, 1943, when the chest tightness returned. At this time the EKG showed absent R in lead IVF with negative T and the chest *x*-ray showed no increase in heart size.

The attacks were mild and irregular until December, 1944, when they increased in severity and frequency, requiring six to eight tablets of nitroglycerin daily for control. Then, following a train wreck, pain and tightness were markedly aggravated and even thirty to forty tablets of nitroglycerin daily failed to give sufficient relief to allow him to venture out of the house. Repeated EKG studies failed to show any change from previous tracings.

Early in June, 1945, thiouracil, .2 Gm. three times daily was started. The initial basal metabolic rate was plus 5 per cent. There was considerable gastric distress from the drug during the first two weeks, but no other reaction was noted. Little improvement occurred during the first eight weeks' treatment, the basal metabolism readings in this period being 0, minus 22, 5 and 13 per cent. In another two weeks, however, there was considerable improvement; he was able to go out for short walks and required only two or three tablets of nitroglycerin daily. The basal metabolism was now minus 16 per cent and the thiouracil was reduced to 0.4 Gm. daily.

At the end of five more weeks the patient was quite comfortable although the basal metabolic

rate was minus 3 per cent. Thiouracil was discontinued for one week and there was a prompt return of symptoms and the basal metabolism rose to plus 7 per cent. Medication was resumed and the distress was relieved in three to four days.

During the next ten weeks the patient remained quite comfortable, requiring only an occasional tablet of nitroglycerin following considerable exertion. The basal metabolism readings during this period were plus 6, minus 9 and plus 11 per cent. The thiouracil was discontinued at this point because the patient was leaving the city. After a little over six months' treatment there was considerable improvement and the patient had gained ten pounds.

Shortly after his arrival in California the attacks of distress recurred and his attending physician prescribed 3 gr. aminophyllin with ¼ gr. phenobarbital four times daily, with nitroglycerin to be taken as needed. He remained symptom-free on this regimen for four months and has been free of all discomfort without any medication since his return home three months ago.

Comment. This patient with severe angina coming on several years after a healed myocardial infarction showed improvement after ten weeks of thiouracil, 0.6 Gm. daily. The initial basal metabolic rate was plus 5 per cent and a level of minus 16 per cent was noted at the time of improvement. Symptoms recurred when the thiouracil was discontinued, and disappeared shortly after it was restarted. There was marked improvement after six months' therapy and a subsequent recurrence was controlled with aminophyllin and sedation given over a period of four months. The patient has been symptom-free without medication for three months.

CASE V. L. N., a fifty-one year old white female, had fully recovered from an attack of acute myocardial infarction in October, 1943, but developed chest pain and tightness on exertion, after meals and emotional stress in June, 1945. She had had a goiter in 1925, with nervousness and bulging eyes, which had responded to ten months' medical treatment. In 1937, a lumbar sympathectomy was performed for hypertension.

She was a plethoric, thick-necked individual with prominent eyes but no true exophthalmos. The thyroid was not palpable. The blood pressure was 170/130, there was grade 2 retinopathy, accentuated aortic second sound, and a rough systolic murmur at the left sternal border. The *x*-ray showed no increase in heart size and the EKG showed left ventricular preponderance. The basal metabolic rate was minus 16, the non-protein nitrogen 33.3 mg. and the cholesterol 210 mg. per cent.

On August 4, 1945, .2 Gm. thiouracil twice daily was started. On August 27th, the basal metabolism was minus 19 per cent and the patient reported no distress or pain. The blood pressure was 140/90. The dosage was reduced to .1 Gm. three times daily and the improvement continued for the next nine weeks with the basal metabolic readings at minus 17, 16, 14, 19, 16 and 12 per cent. The blood pressure ranged between 140 and 148 systolic and 100 to 110 diastolic.

Within another four weeks, as cold weather set in, there was gradual recurrence of pain and distress and the thiouracil was gradually increased to .6 Gm. daily. The basal metabolic readings were minus 8 and minus 11 per cent and the blood pressure had returned to 170/110. After two weeks on the increased dosage, improvement occurred and the basal metabolism dropped to minus 20 per cent while the blood pressure receded to 150/80, then 130/80, and 120/80. In another four weeks the basal metabolism was minus 23 per cent, there was puffiness of the face and eyes and the patient complained of extreme sensitivity to cold. The blood cholesterol was 369 mg. per cent. Thiouracil was reduced too 0.4 Gm. daily and the puffiness gradually receded while the patient remained totally free of discomfort.

Treatment was discontinued after a total of seven months and within a week there was recurrence of all former symptoms. At this time the EKG and the chest *x*-ray showed no change. Propyl-thiouracil was now started but a dosage of 25 mg. three times daily for three weeks failed to control the disturbance. A greater measure

of relief followed when the dose was increased to 25 mg. five times daily but the control was not as good as that obtained with thiouracil. This level was continued for seven weeks during which the basal metabolic rate was minus 16, 10, 11, 12 and 10 per cent. It was planned to increase the dosage but the sudden death of a brother with angina precipitated a marked increase in pain necessitating hospitalization and oxygen administration for relief. EKG studies failed to reveal evidence of myocardial infarction.

Comment. This patient with severe angina and hypertension, who had formerly recovered from an acute myocardial infarction, showed improvement after three weeks of thiouracil 0.4 Gm. daily. The basal metabolic rate dropped from minus 16 to minus 19 per cent. On reducing the drug to 0.2 Gm. daily, symptoms returned and the basal metabolism rose to minus 8 and minus 11 per cent. When increased to 0.6 Gm. daily, improvement recurred and the basal metabolism dropped to minus 20 per cent, then to minus 23 per cent, when myxedema developed. On a maintenance dose of 0.4 Gm. daily the patient remained symptom-free. After seven months' treatment, thiouracil was stopped and symptoms recurred within a week. Propyl-thiouracil was substituted for ten weeks but the dosage was insufficient for control comparable to that obtained with thiouracil.

CASE VI. O. H., a forty-two-year old white male, had been having attacks of precordial pain and distress for nearly two years. These were most severe upon exertion following a meal, with the pain radiating into the throat and left shoulder and arm. Relief at first followed rest; later nitroglycerin became necessary; more recently the ineffectiveness of both these measures kept the patient from his work.

Examination disclosed an accentuated second aortic sound, a rough systolic murmur at the left sternal border and a blood pressure of 148/90. *X*-ray study showed no cardiac enlargement although there was some increase in prominence of the aorta. The EKG showed left axis deviation; Q_1 and Q_2; depressed ST_1 with diphasic T_1; low voltage; positive T_2 and T_3 and absent R_3. The precordial leads showed absent RCF_2 with elevated ST and positive T; deep QCF_4, elevated ST and negative T; QCF_5 with depressed ST and negative T. The basal metabolic rate was plus 6 per cent.

Thiouracil, .2 Gm. three times daily, was started in August, 1945. In six days the patient developed generalized joint pain and headache which continued for four days. No thiouracil was taken for eight days then it was resumed at the lower level of .1 Gm. three times daily. No further reaction occurred.

Four weeks after beginning treatment the patient had returned to part-time work because his attacks of pain were fewer and less severe. The basal metabolism was minus 9 per cent. In another two weeks improvement was still more marked and full-time work was resumed. The basal metabolism was now minus 19 per cent. The drug was reduced to 0.1 Gm. twice daily and continued at this level for the next eight weeks, the basal metabolic readings being minus 9, 16 and 6 per cent. Coincident with the last reading there was reported a return of distress and medication was increased too 0.1 Gm. three times daily.

In the following eighteen weeks the patient was able to continue regularly at his work without notable discomfort. The basal metabolic readings during this interval were minus 13, 11, 19, 22 and 20 per cent. At this point, after eight months' continuous treatment, both lobes of the thyroid became palpable but there were no signs of myxedema. Thiouracil was discontinued but pain recurred within two days and became more marked during the next four days. Propyl-thiouracil, 25 mg. four times daily, was substituted and improvement followed after two days. This treatment was continued for twelve weeks during which there was very little discomfort and the basal metabolism was minus 23, 3 and 9 per cent. Propyl-thiouracil was discontinued and eleven months of anti-thyroid therapy terminated. The patient has continued symptom-free for one month. The EKG showed no change.

Comment. This patient with severe angina developed a drug reaction six days after starting 0.6 Gm. thiouracil daily. After a weeks' abstinence he was able to take 0.3 Gm. daily without difficulty. Improvement was noted first after four weeks and was more pronounced at the end of six weeks with corresponding basal metabolic readings of minus 9 and minus 19 per cent. Bilateral thyroid enlargement was noted after eight months' treatment. Reduction of the drug to 0.2 Gm. daily and its discontinuance allowed pain to recur. Propyl-thiouracil, 100 mg. daily, successfully controlled the disturbance for three months. After eleven months' anti-thyroid treatment the patient has remained free of angina for one month without any medication.

Case vii. J. K., a sixty-year old white female, had hypertension for two years previous to an attack of acute posterior myocardial infarction in February, 1944. Recovery was uneventful but in September she began having occasional attacks of precordial pain following exertion and relieved by rest. Gradually these attacks became more severe and frequent in spite of continuous administration of aminophyllin and sedatives, and required six to eight tablets of nitroglycerin for their control. They would follow each meal and would come on after walking a short distance. Pain was now referred to the throat and the left shoulder and arm.

Examination showed forceful heart sounds, accentuation of the aortic second sound and a blood pressure of 140/90. The EKG showed left axis deviation with absent R in leads 3 and 4F and elevated ST with diphasic T in this latter lead. The basal metabolism was minus 6 per cent.

In September, 1945, thiouracil 0.1 Gm. three times daily, was started with little improvement during the following month. The basal metabolism was now minus 8 per cent. In another month, however, there was considerable improvement, the attacks being fewer and less severe with the need for nitroglycerin much reduced. The basal metabolism was now minus 16 per cent.

Thiouracil was discontinued at this point but within a week there was a marked increase in pain and discomfort so medication was resumed, with relief following in three to four days. She continued to improve steadily during the following three months and after a total of six months' therapy had very little discomfort and no longer needed nitroglycerin. The basal metabolic readings during this period were minus 12, 16 and 19 per cent.

Propyl-thiouracil, 25 mg. four times daily, was substituted for the thiouracil without change in the patient's condition. During the three months it was given the basal metabolism was minus 20, 19 and 17 per cent. She has been symptom-free for one month on no medication.

Comment. This patient with moderately severe angina developing several months after an attack of myocardial infarction showed improvement after two months of thiouracil, 0.3 Gm. daily. The initial basal metabolism was minus 6 per cent and at the time of improvement it was minus 16 per cent. Symptoms recurred when the thiouracil was discontinued and improved when it was resumed. Marked improvement was attained at the end of six months and this was sustained for another three months with 100 mg. daily of propyl-thiouracil substituted for the thiouracil. The patient has remained well for one month without any medication.

Case viii. S. D., a fifty-eight-year old white male, developed attacks of precordial tightness with radiation to the throat upon exertion five years after he had recovered from an acute anterior myocardial infarction. These increased in frequency and nine months after the onset required five to six tablets of nitroglycerin for their control.

On examination the patient was about twenty pounds overweight, the heart sounds were distant with no audible murmurs, and the blood pressure was 100/80. The EKG showed a small Q_1, negative T_3, absent R and elevated ST with upright T in CF_2 and CF_4, and a QCF_5. The basal metabolism was plus 2 per cent.

On October 9, 1945, thiouracil, .1 Gm. three times daily, was started. There was little change during the first month although the basal metabolic rate had dropped to minus 9 per cent. At the end of another month the patient reported very little distress requiring only an occasional tablet of nitroglycerin. The basal metabolism was now minus 12 per cent. The patient failed to report for further observation.

Comment. In this instance of mild angina coming on several years after an acute myocardial infarction, there was apparent relief after two months of thiouracil, 0.3 Gm. daily. The basal metabolic rate had dropped from plus 2 to minus 12 per cent. However, the period of observation was too brief to permit classification of the result.

SUMMARY

Of eight patients with angina treated with thiouracil, five were improved, two unimproved, and one, though showing some evidence of improvement, had not been observed long enough to permit classification of the result. The two that did not respond were treated for three months and six weeks respectively. One of these, with severe angina, showed a change in the basal metabolic rate from minus 15 to minus 18 per cent. The other, with mild angina, dropped from plus 1 to minus 2 per cent. The patient with the unclassified result had a mild angina, was treated for two months, the metabolism changing from plus 2 to minus 12 per cent.

By contrast, the five who improved were treated for eight, six, seven, eight and six months, respectively, an average of seven months. Little if any improvement became manifest before two months had elapsed. The lowest basal metabolic levels reached in these patients were minus 24, 22, 23, 23 and 20 per cent.

In patients B. W. and L. B. myxedema developed at four months and five months, respectively. Bilateral thyroid enlargement appeared in patient O. H. at the end of eight months' treatment. This constitutes valid evidence for the ability of thiouracil to suppress the normal thyroid if it is administered consistently over a long enough period of time.

Toxic reactions to the drug offered little interference in the treatment of this small group. Patient M. C. developed gastric distress at the onset which disappeared quite promptly. Patient O. H. developed joint pains and headache on the sixth day, which cleared on stopping medication for one week and did not recur on a lower dosage level.

Propyl-thiouracil, because of its lesser toxicity, was substituted for thiouracil in three patients after improvement had appeared. In patient L. B. three months' administration at 75 to 125 mg. daily failed to hold the gain made with thiouracil. One hundred mg. daily over a three months' period held the ground previously gained by patients O. H. and J. K..

Four of the five improved patients continued symptom-free without further treatment: Patient B. W. for four months, patient M. C., three months, and patients O. H. and J. K. one month each. In accounting for this and the improvement in general, it may well be claimed that a period of time alone, comparable to that devoted to treatment with thiouracil, would be sufficient to permit development of enough collateral circulation to overcome the anoxia and pain. While this might account for the ultimate improvement and freedom from attacks after treatment had been terminated, it would make no allowance for the part played by the thiouracil in lowering the metabolism, reducing the demands on the heart muscle, and in decreasing the latter's sensitivity to adrenalin. This action, though slow in developing, is apparently instrumental in controlling the symptoms in

angina while modification of existing circulatory deficiencies is being accomplished through improvement in the collateral circulation.

CONCLUSION

From the data obtained in the above study it is fair to conclude that thiouracil exerts a suppressive action on the normal thyroid when given over a long enough period of time, and effects chemical thyroidectomy benefitting the patient with angina pectoris.

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The Effects of Quinacrine (Atabrine) Suppression on the Course of Pacific Vivax Malaria*

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THE studies reported here were designed to determine the effect of quinacrine suppression on the course of recurrent Pacific vivax malaria in a non-endemic area.

MATERIAL

Group A. Forty-nine patients were treated at this hospital for acute attacks of vivax malaria of Pacific origin with 2.8 Gm. quinacrine in seven days and were then placed on a suppressive regimen of 0.1 Gm. quinacrine daily for 150 days. Medication was administered under supervision to insure ingestion of the drug. During the period of suppression, thick malaria smears were examined weekly. Fasting plasma quinacrine levels were determined[1] every two weeks during and for one month after the period of suppression.

Group B. As a control group, sixty-nine patients were treated for acute attacks of Pacific vivax malaria with 2.8 Gm. quinacrine in seven days without subsequent suppressive medication.

Group C. Four hundred four patients who were treated for acute attacks of Pacific vivax malaria provided information on the relationship of the incidence of recurrence to the number of previous attacks. Quinacrine, chloroquine (SN 7618),[2,3] or quinine in various dosage regimens were used in treatment of these attacks.* The sixty-nine patients in Group B are included in this analysis. The patients are divided into five groups: (1) 116 patients who had had no previous attacks of malaria; (2) 186 patients with one to five previous attacks; (3) forty-nine patients with six to ten previous attacks; (4) forty patients with eleven to twenty previous attacks; and (5) thirteen patients with twenty-one or more previous attacks. The incidence of recurrence within 120 days in each of these groups was determined.

Following the end of antimalarial medication, whether for suppression or for treatment of an acute attack, all patients (Groups A, B, and C) were observed until the first subsequent relapse, or, if no relapse occurred, for 120 days. During this period of observation, thick malaria smears were examined once or twice weekly. No antimalarial therapy was administered except

* The drug regimens were as follows: quinacrine, 2.8 Gm. in seven days (1.0 Gm. the first day and 0.1 Gm. three times a day for six days), 2.2 Gm. in three days (1.0 Gm. the first day and 0.6 Gm. daily for two days); chloroquine, 2.0 Gm. in seven days (0.8 Gm. the first day and 0.2 Gm. daily for six days), 1.0 Gm. in one day, 0.8 Gm. in seven days (0.2 Gm. the first day and 0.1 Gm. daily for six days), 1.5 Gm. in four days, (0.6 Gm. the first day and 0.3 Gm. daily for three days), and 1.5 Gm. in three days (0.9 Gm. the first day and 0.3 Gm. daily for two days); and quinine sulfate, 29.0 Gm. in fourteen days (3.0 Gm. the first day and 2.0 Gm. daily for thirteen days).

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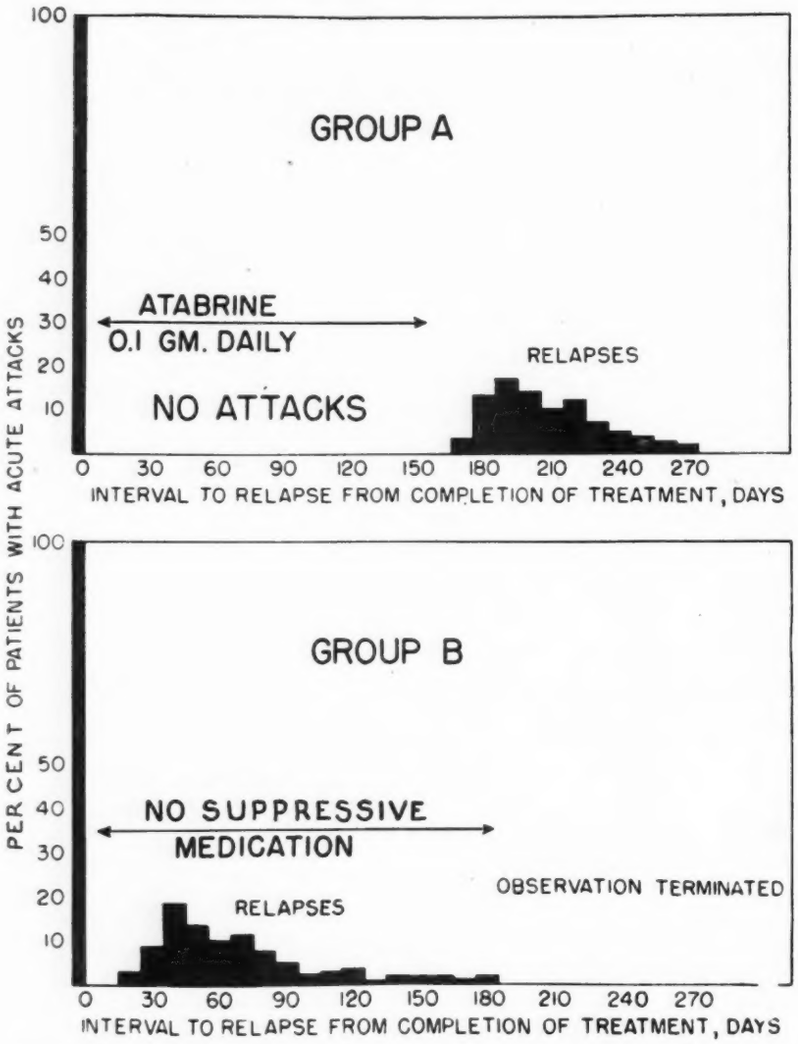

FIG. 1. Distribution of relapses in two groups of patients following treatment for acute attacks of vivax malaria of Pacific origin. Group A was placed on suppression medication 0.1 Gm. quinacrine daily for 150 days after treatment of the acute attack. Group B was treated for the acute attack but did not receive subsequent suppressive medication. Each group was observed for 120 days following the end of antimalarial medication. Note the absence of relapses in Group A during the period of suppressive medication and the similarity in the time distribution of relapses and in the rates of relapse in both groups during the 120-day observation periods.

for treatment of a clinical relapse. A patient was considered to have a clinical relapse when he had a smear positive for malaria parasites in association with an oral temperature above 100°F.

RESULTS

1. *Immediate Effect of Suppression.* During the 150 days of suppression, none of the forty-nine patients in Group A had either asymptomatic parasitemia or a clinical relapse. The mean of the individual mean fasting plasma quinacrine levels of this group during the five months of suppression was 19 micrograms per liter.

2. *Course of Disease Following Suppression.* During the 120-day period of observation following cessation of suppressive medica-

tion, 82 per cent of the patients in Group A had a clinical relapse. This is nearly identical with the 80 per cent incidence of relapse observed in the 120 day period following treatment without suppression in control Group B. (Fig. 1.) The distribution of relapses in relation to the time following the end of suppressive or therapeutic medication is essentially the same in both groups.

Of ten patients in Group A whom we were able to observe again following treatment for the attack which terminated the first observation period, eight had another relapse within 120 days.

3. *Relationship of Incidence of Recurrence to Number of Previous Attacks.* This relationship is presented in Table 1:

TABLE 1
RELATIONSHIP OF NUMBER OF PREVIOUS ATTACKS TO INCIDENCE OF RECURRENCE WITHIN 120 DAYS FOLLOWING TREATMENT OF 404 ATTACKS OF PACIFIC VIVAX MALARIA

No. of Previous Attacks	No. Men Treated	Clinical Relapses within 120 Days	
		No. Men	Per Cent
0	116	81	70
1–5	186	135	73
6–10	49	38	78
11–20	40	29	73
21 or more	13	6	46

These data indicate that recurrence at a rate of 70 to 80 per cent in 120 days following treatment with quinacrine, chloroquine or quinine obtains in all groups of patients, except perhaps for a small number who have had a great many previous attacks (over twenty) and in whom the disease may "die out" more abruptly.

DISCUSSION

Our experience with large numbers of patients whom we have treated for acute attacks of Pacific vivax malaria with quinacrine, chloroquine or quinine indicates that approximately 70 to 80 per cent of these patients have a recurrent attack within 120 days.[3,4] It is reasonable to assume, therefore, that the course of the disease, in the strains of Pacific vivax malaria which we have treated, is one in which 70 to 80 per cent of patients will relapse within 120 days after treatment of an attack with quinacrine, chloroquine or quinine, and that of the patients who have relapsed, 70 to 80 per cent will have still another attack within another period of 120 days following similar treatment. It is generally accepted that vivax malaria dies out usually within two years after the last infection.[5]

Our experience with patients whom we have been able to follow through more than one attack may be cited in further support of the view that recurrence at a rate of 70 to 80 per cent within 120 days is characteristic of Pacific vivax malaria. Of 321 men treated with quinacrine, chloroquine or quinine for acute attacks, 75 per cent relapsed within 120 days. Of these, 120 men were observed again and 70 per cent of them had another attack within 120 days following the previous attack. Of this latter group, thirty-three men were followed for another period of 120 days and 70 per cent of them had a third recurrent attack under our observation.

It is recognized that this characteristic relapse rate of 70 to 80 per cent within 120 days is arbitrary inasmuch as the 120 day observation period was chosen arbitrarily. This period was chosen because it was found to be sufficiently long to include the great majority of recurrent attacks and was found at the same time to be a practical period for study of military personnel. We are aware that not all patients who relapse do so within 120 days, and, accordingly, that not all of the 20 to 30 per cent who do not relapse within 120 days represent complete cures. However, of any large group

treated with quinacrine, chloroquine or quinine, a portion of the 20 to 30 per cent, although it may be small, will have no further relapses. This is supported by the fact that the majority of any large group of patients is cured of the disease within eighteen months after the last infection.

The patients in this study were treated and admitted to the various groups as their attacks of malaria occurred, and no attempt at selection of cases was made. It is believed that this procedure minimized the influence on the rate of recurrence of factors such as differences in the severity of the original infection (i.e., the number of sporozoites introduced into the human host by the infected mosquitoes) and differences between parasite strains which may be responsible for individual variations in the frequency of relapses and in the total duration of the infection.

Our data indicate that the course of recurrence at a rate of 70 to 80 per cent in 120 days applies to patients following cessation of suppression as well as to patients who have been treated for an acute attack without subsequent suppressive medication. Of the ten patients in Group A whom we were able to observe for an additional period of 120 days following relapse, eight had recurrent attacks. Furthermore, nearly all of the malaria patients whom we treated in this hospital had received suppressive medication while overseas. As has been noted, they have followed a course of recurrence at the rate of 70 to 80 per cent within 120 days since the discontinuance of suppression.

The 82 per cent rate of recurrence within 120 days after the 150-day period of suppression demonstrates that complete suppression *per se* does not produce a diminished rate of relapse following the discontinuance of suppressive medication. These data may be interpreted as indicating that complete suppression has not shortened the course of the disease in these patients, and, indeed, the possibility is raised that such suppression may hold the course of the disease in abeyance and thus may delay complete cure and prolong the duration of the disease in a group of patients. The exigencies of military service did not permit us to continue observation of the suppressed and unsuppressed groups throughout the course of their disease until complete cure of all patients in the groups had been achieved. Consequently, we have no conclusive demonstration that the total duration of the disease in a suppressed group is or is not prolonged.

It must be stressed that our data apply only to complete suppression for 150 days with 0.1 Gm. quinacrine daily in a non-endemic area. It is quite possible that during suppression under less well controlled conditions, the disease will continue to run its course in some patients because of mild attacks permitted by inadequate suppressive medication. Consequently, studies of incidence of attacks in such groups of men may in fact reveal a diminished relapse rate after cessation of suppression. It is conceivable that complete suppression for longer than five months might result in a diminished relapse rate after discontinuance of such suppression, and that complete suppression for as long as two years might eradicate the disease. There is as yet, however, no experimental evidence in support of such effects.

In the absence of conclusive evidence of the effect of complete suppression on the duration of the disease, the routine use of suppressive quinacrine medication for long periods in a non-endemic area seems at present inadvisable, particularly since such medication is not without danger. Serious toxic manifestations in the skin and hematopoietic system (lichen planus and eczematoid dermatitis,[6] aplastic anemia[7]) occur in a small percentage of individuals who receive prolonged suppressive quinacrine medication. Although the toxicity of chloroquine

administered for many months is not yet clearly defined, it is known that one may encounter toxic reactions on prolonged medication.[2] The rational use of quinacrine or chloroquine for treatment of acute attacks, however, does not entail similar toxicity. Furthermore, when properly used, these drugs control acute attacks rapidly and permit early return to full activity. So long as the effect of prolonged suppression on the duration of the disease is not clearly delineated and prolonged suppressive regimens may produce toxicity, we believe it is preferable to treat acute attacks in unsuppressed patients rather than to use suppressive medication for long periods.

In the light of the studies and considerations which have been reported here and elsewhere,[2,3] the following suggestions are made for the management of cases of recurrent vivax malaria of Pacific origin. Acute attacks should be treated with chloroquine or quinacrine. If a patient has had numerous debilitating attacks at frequent intervals since leaving the endemic area, it is suggested that a subsequent attack be treated with the combined quinine-plasmochin or quinine-pentaquine fourteen-day regimens. These regimens have been shown to be curative in a high percentage of cases. Indications, dosage and necessary precautions in the use of these regimens have been presented elsewhere.[8,9]

It is further suggested that prolonged suppressive medication not be used routinely in a non-endemic area. It should be emphasized that this recommendation is not meant to apply to endemic areas, particularly in time of war when the fighting efficiency of an army exposed to malaria depends on effective suppression. In a non-endemic area, however, suppression is not advisable except in cases of intercurrent illness or in cases in which it is imperative that there be no absence from work during a limited period. Occasionally, it may also be advisable in prolonging the interval between recurrences in patients who are suffering from frequent attacks and who cannot spend fourteen days in the hospital as required by the quinine-plasmochin or quinine-pentaquine regimens.

SUMMARY AND CONCLUSIONS*

Quinacrine, 0.1 Gm. daily, was administered to forty-nine patients for 150 days following quinacrine treatment of an acute attack of Pacific vivax malaria. This dose was effective in suppressing completely parasitemia and clinical attacks. In a period of 120 days following termination of suppression, 82 per cent of the men had a recurrence of malaria. This incidence was the same as was found in a control group of sixty-nine men who were observed for 120 days following quinacrine treatment of the acute attack without subsequent suppressive medication. This and other evidence cited indicate that the course of the disease is not shortened by complete suppression and the possibility is raised that the duration of the disease may be prolonged. In the light of the considerations presented in these studies, routine suppression for prolonged periods in a non-endemic area is not recommended.

Recommendations for the management of Pacific vivax malaria in a non-endemic area are made.

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"Muscle Spasm" in Acute Low Back Pain and Similar Syndromes*

A New Method of Treatment with Curare (d-Tubocurarine in Oil and Wax)

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THE entity clinically designated as "muscle spasm" is an integral part of many of the common wear and tear syndromes of every day practice. The term is loosely used but roughly may be defined as a state of transient muscle contraction, not amenable to voluntary control, characterized by resistance to stretch and usually associated with pain on attempted extension.

Clinically, the picture is well recognized. It may be a muscle response to irritation, whether inflammatory or traumatic. It may be reflex in origin and secondary to pathological conditions, visceral or somatic, of like segmental neural connection. Kellgren,[1] Wolff[2] and others have shown that this latter type of muscle spasm may be perpetuated after cessation of the initiating stimulus and thus present a major treatment problem.

The various lesions which together make up the low back syndrome are excellent examples of the importance of the problem of muscle spasm in treatment. The initiating trauma or etiologic agent is followed by muscle splinting as a protective measure. Pain enhances the splinting or spasm, which in turn is followed by more severe pain and further muscle spasm. The vicious cycle is self-perpetuating. Whether the intense pain is at least partly ischemic in origin is not fully understood.

Dramatic relief may be afforded by any agent which tends to interrupt and break up the cycle of splinting and pain. There are many traditional measures, all of which have some rationale and serve their purpose, at times, admirably. These include heat, traction, ethyl chloride spray, novocaine or saline injections, and heavy sedation. Unfortunately, none of these measures is specific or generally reliable in a series of cases.

Since curare is known to create a myoneural block, it is logical to try to apply its properties to the treatment of muscle spasm. Unfortunately, in aqueous solution its action is evanescent, with poor control of blood levels, and its therapeutic margin is narrow, particularly in the ambulatory or casually observed patient. A newer preparation, tubocurarine in oil and wax,† previously described by one of the authors,[3,4,5] circumvents to a great extent these therapeutic limitations by providing slow absorption at fairly predictable levels of saturation. In previous reports, it has been shown that with this preparation it is possible to create a partial block at the myoneural junction without loss of voluntary function or any unpleasant curare side effects.

The series of cases presented in this paper has been treated with the aforementioned

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TABLE I

ACUTE LOW BACK DISORDERS OR SIMILAR SYNDROMES

I. Associated with structural abnormalities, such as osteoarthritis and congenital or acquired deformities.

Name	Diagnosis	Symptoms and Signs	Previous Treatment	Response to Curare	Reaction
H. H.	Acute low back strain, sacralisation L_5 with osteoarthritis	Severe low back pain Marked splinting Loss normal lordosis	Traction Heat Morphia	Complete relief of diffuse severe pain with muscle relaxation in 2 hrs. Pain now localized to L_5 body on movement only	None
L. T.	Kyphosis and scoliosis upper thoracic spine	Constant pain and aching with muscle spasm T_4 region and spinatus group	Massage	Relief of pain and aching discomfort	Diplopia 1½ hrs.
H. S.	Osteo arthritis spine with acute low back strain	Severe generalized low back pain with immobility, some sciatic radiation	Diathermy Static wave	Relief of severe pain Residual soreness Loss sciatic pain	Dizziness 2 hrs.
C. D.	Unstable back with sacralisation L_5, acute low back strain	Loss lordosis Immobility of back Severe generalized pain	Ethyl chloride Heat	Subsidence of generalized pain, residual aching in sacral region	Diplopia 1 hr.
L. R.	Lumbosacral osteoarthritis with scoliosis. Degenerative disease of the intervertebral disc with narrowing	Weak back for years Severe low back pain 2 months with occasional radiation to rt. leg	Heat	Relief of severe pain in 2 hrs. Slight soreness low back	Drowsy next day
E. Y.	Osteoarthritis cervical spine with cervical 'myositis'	Splinting trapezii, erector capitae Lack of mobility of head and shoulders	Heat Massage	Relief of pain Marked increase in mobility. Residual soreness	None
L. M.	Infarct vertebral body L_4 (sickle cell)	Splinting lumbosacral muscles with immobility and severe pain	Heat Bedboards	Reduction of spasm, able to move about, pain localized to site of pathology	None
H. S.	Acute low back strain, osteoarthritic changes with degenerative disc disease and narrowing of lumbar interspaces	Severe generalized pain with marked lumbosacral tilt, immobility of lumbar spine	Heat Corset Massage	Relief of generalized pain, increased mobility	Diplopia 1 hr.
E. S.	Osteoarthritis cervical spine with spurs	Severe neck and shoulder girdle pain, limitation of movement, headache	Diathermy Massage	Relief of constant pain and headache in 2 hrs. Residual soreness, increased mobility	None

II. With no demonstrable structural abnormalities.

K. K.	Acute low back syndrome	Severe lumbosacral pain with tilt to right Loss of lordosis, left sciatic pain, immobility	Heat Morphia	Dramatic relief in 3 hrs. of sciatic and low back pain Residual soreness	None
H. B.	Autonomic disturbance with trapezius, erector capitae and shoulder girdle muscle spasm	Severe neck and shoulder pain radiating down arms. Immobility of neck	Morphia Heat Massage	Marked relief, residual soreness	None

TABLE I (*Continued*)

Name	Diagnosis	Symptoms and Signs	Previous Treatment	Response to Curare	Reaction
III. Following operation for removal of herniation of nucleus pulposus.					
H. B.	Post-op. herniated nucleus pulposus with low back syndrome, recurrent, and pyelitis C	Severe erector spinae spasm with complete immobility of low back and generalized pain	Heat Morphia Massage	Increase in mobility Loss of excruciating pain, residual soreness marked	None
H. H.	Post-op. laminectomy for herniated nucleus pulposus	Excruciating generalized low back pain; immobility of spine, loss lordosis	Corset Heat Novocaine Morphia	Dramatic complete relief in 2 hrs. Able to move about freely, soreness in muscles of low back	None
J. G.	Post-op. herniated nucleus pulposus Recurrent pain and muscle spasm of glutei and paravertebral muscles	Immobility, generalized low back pain	Heat Bedboards Massage	Relief generalized pain, increased mobility, 'pain now in bones"	Diplopia few minutes
IV. Associated with nerve root compression.					
D. W.	Herniated nucleus pulposus narrowing of interspace	Low back pain, ? sciatic radiation, and abdominal distention	Morphia Traction Bedboards	No relief, accentuation segmental distribution of sciatic pain	None

curare suspension, usually after conventional methods have failed. It has been consistently possible to break up muscle spasm and enhance recovery rate when the initiating pathological condition is static or brought under control. Where the pain and local muscle spasm were secondary to a continuing stimulus, i.e., root compression, radicular pain persisted after reduction of the spasm and the local or reflex spasm often recurred shortly. This response may prove to be a useful diagnostic test and will be discussed later in the paper.

The cases studied run the gamut of low back disorders, including the usual orthopedic disturbances, so-called low back strain, osteoarthritis of the spine, actual vertebral lesions, disc lesions and also some instances showing reflex spasm secondary to remote disease. Table I is a compilation of typical cases and results.

It is apparent from a perusal of the above data that in many cases of low back syndrome an abrupt cessation of the major complaints often follows upon relief of muscle spasm. The sequence of events after treatment is of interest. The patient usually notes an abrupt relief of major pain within several hours after injection. Mobility is increased and the patient often describes a feeling of pleasurable relaxation, even drowsiness. The severe pain is followed by muscle soreness and localized pain in the region of actual disease, if it is capable of local signature. The soreness is a logical sequel, since protracted muscle contraction is associated with diminished vascular exchange and ischemia. It is known that, depending upon the chronicity of the process, the muscle involved may thus show reversible inflammatory changes, cloudy swelling, etc. The characteristic tenderness which remains even after complete relief of pain seems to have its basis in this transient pathologic state.

Three case histories are described in detail since they are representative of the general results:

CASE REPORTS

CASE I. H. H., a forty-eight-year old male, member of a medical college faculty, over a period of years has had occasional lumbosacral pain with moderate muscle spasm. These attacks were self-limited and disappeared without residue. In recent years, the patient had grown much heavier and had led a more sedentary existence. In February, 1946, he began to note recurrence of lumbosacral pain. This became increasingly severe over a period of days and he was admitted to the hospital. On mild sedation, bed boards and rather haphazard traction, he improved enough in three days to be discharged. *X*-ray examination had revealed an unstable lumbosacral joint with proliferative arthritis in the joint region.

Two days later pain had increased to its former severity and the patient was again hospitalized. Muscle spasm at this time was more pronounced, and the patient was in constant severe discomfort in all positions. Traction was reinstituted without relief. Morphia and sedation were used in large doses. The orthopedic consultant advised a body spica, full length, and this was applied. The patient complained more and more bitterly, remained sleepless and unrelieved by any form of medication. At the end of four days, spinal anesthesia was contemplated in a heroic attempt to reduce the marked muscle spasm of the entire low back region with the accompanying severe pain. A trial of curare in oil was agreed upon instead. One cc. of the suspension was given in the right buttock. Two hours later, the patient stated that his back muscles had relaxed and at the same time the accompanying generalized pain had vanished. The reduction in muscle spasm was immediately demonstrable on examination. The patient now noted only focal pain on motion at the lumbosacral articulation. Relief of pain was followed by adequate rest without medication. The patient became less tense, began to eat and regain his normal equilibrium. However, by the third day, in dread of a recurrence, he requested a second injection. The same dose of drug was given at this time and again three days later. The spasm never recurred and the patient's subsequent convalescence was completely uneventful. A back brace was prescribed by the orthopedist and when this was fitted, the patient was allowed up and discharged from the hospital.

CASE II. K. K., a fifty-year old woman, was admitted as an emergency because of excruciating low back pain with left sciatic radiation. She was unable to move about without evoking showers of pain throughout the lumbosacral region and down the left leg. She lay in bed with the low back characteristically immobile, and the left leg supported on pillows at the knee. Examination was impossible because of the extreme pain and *x*-ray examination could not be carried out. Conventional medication afforded minimal relief. One cc. of *d*-tubocurarine in oil was injected in the left gluteal region and in two hours the patient had noted an almost complete cessation of pain. She was able to move about and physical examination and *x*-rays were performed. There was no evidence of nerve root compression on examination. *X*-rays showed normal low back structures but an arthritic process about the hip joint. As the pain and muscle spasm of the low back diminished, the sciatic reference of pain gradually disappeared. Within three days, the patient was up and about her room and shortly was discharged free of symptoms.

CASE III. D. W., a fifty-four year old male, had had recurrent attacks of low back pain since he lifted a heavy weight some time ago. On admission, he complained of severe lumbosacral pain with radiation to the right knee. When standing, his posture was stooped, with the low back immobile and the right leg flexed protectively at the knee. There was marked splinting of the erector spinae muscle group. On traction, heat and bed boards, he developed abdominal distention of such degree that intubation was necessary. Prostigmin and pitressin afforded no relief. In the hope that curare might reduce his low back signs and therefore ameliorate the reflex distention, he was given 0.9 cc. of *d*-tubocurarine in oil and wax, intramuscularly. Coincidentally, and with vigorous treatment, the distention was relieved.

After curare, the patient noted definite sciatic distribution of pain on coughing and sneezing and the segmental nature of his leg pain became objectively more evident. At operation, subsequently, a large protruded herniation of the nucleus pulposus was found at the fourth lumbar interspace on the right.

These cases are cited to delineate the value of the response to curare therapy as a diagnostic test. As described above, relief of muscle spasm ordinarily is followed by abrupt relief of local pain and its reference. However, where root compression, such as in herniation of the nucleus pulposus, is the exciting and continuing stimulus, the relief of local muscle spasm does not influence the severe pain and actually may highlight its segmental nature by removing temporarily the purposeful splinting action of the muscle spasm.

Several cases are included in Table 1 in which the pathological process is very similar but of different anatomical distribution. Where the same criteria are met, the results are much the same. However, it should be stressed that muscle spasm of the erector capitae and trapezius groups is more difficult to treat, since these muscles are seldom out of use and unless specifically prescribed, are difficult to put at rest. Strict bed rest is of major importance to successful therapy.

Among all the pathological entities which may be classified as "wear and tear" syndromes, rheumatoid arthritis seems the most refractory to treatment. There are few, if any, specific therapeutic measures. It has seemed worth while to evaluate the effect of curare in the acute phase of the disease, since to the clinician at this stage there are changes similar to skeletal muscle spasm. The authors are fully aware of the danger involved in the indiscriminate use of the term "muscle spasm." So far as the aforementioned conditions are concerned, the entity is clear-cut. In rheumatoid arthritis there is a very similar clinical picture, arising perhaps out of different mechanisms. Several factors are at play. In addition to joint inflammation, there may be infiltration of the actual muscle mass by inflammatory exudate. Freund et al.[6] have described lymphorrhagic infiltrations in the peripheral nerves. All these irritative phenomena apparently either directly or reflexly give rise to the extreme pain on attempted stretch or attainment of full range of motion.

The typical protective position adopted in an attempt to prevent pain is a major cause of deformity, reversible early but static in the later stages of the process. Long periods of fixation, with unwillingness to perform normal movements because of intense pain, lead to atrophy of disuse and fibrosis.

The clinical goal is, first the prevention of long standing protective splinting with subsequent muscle changes and disturbances of joint function, and secondly, the alleviation of pain. In early cases, it has been routinely possible to influence favorably the characteristic flexion deformity during the period of treatment. Pain in these cases is based upon a complex combination of factors, but with relief of abnormal muscle tension there seemed to be a gratifying diminution in pain. Major forms of analgesia could be discontinued and the residual pain controlled well with traditional medication such as aspirin.

The following case reports illustrate the type of disorder amenable to treatment and the therapeutic results obtained.

CASE IV. E. S., a twenty-five-year old woman, suffered with severe rheumatoid arthritis for six months. On admission her sedimentation rate was markedly elevated and agglutination with hemolytic streptococcus group A was positive. Flexion contracture of both elbows was present with extension possible only to 110 degrees, with severe pain supervening beyond this range. Her fingers were characteris-

tically fusiform. The patient was admitted to the hospital partially curarized over a period of four days with 1 to 1.1 cc. of *d*-tubocurarine in oil and wax daily. After saturation with drug, her elbows could be extended completely without pain. She was given two transfusions with whole blood, gold therapy was started, and she was discharged to the clinic where curare was continued twice weekly and later weekly. Exercise was encouraged. At the present time she is free of pain, has complete extension of elbows and knees and sleeps soundly. She is ambulatory, carries out her housework and drives a car. Of interest is the fact that she has very little atrophy of the small muscles of the hand at present. During the course of treatment she noted slight drowsiness on several occasions and diplopia momentarily on one occasion.

CASE V. D. D., a male of thirty, had had an acute onset of peripheral joint and back pain two months before admission. One year and again four months previously, he had been treated successfully for gonorrheal urethritis. At another hospital massive quantities of penicillin had been injected intramuscularly and into a knee joint without benefit to his present complaints. On admission he was in marked distress with flexion contractures of both elbows to 85 degrees and of both knees to 100 degrees. These could be overcome passively only very slowly and with much pain to the patient. Spine *x*-rays showed changes in three of the apophyseal joints of the lumbar spine and in the right sacroiliac joint. Examination of the peripheral joints showed no heat, redness or swelling, and *x*-rays were negative. The patient ran a fever of 101°F. daily and for four days was treated with analgesics. Pain remained severe and sleep was very poor on 200 to 250 mg. of demerol daily. He was started on 1 cc. of *d*-tubocurarine in oil and wax daily and by the third day pain could be well controlled with aspirin and codeine. He was able to extend his arms and legs actively. Partial curarization was maintained and he was started on *x*-ray therapy, on which treatment he showed a marked exacerbation of symptoms. During curare treatment, the patient noted double vision on one occasion for about thirty minutes, but no other side effects were encountered.

In recognition of the difficulty in assaying therapeutic results in rheumatoid arthritis, the apparent beneficial effect of curare must be interpreted with caution. However, results are sufficiently encouraging to warrant extension of the present study. An attempt is being made to support clinical impressions by objective measurements. It is hoped that a larger body of cases with objective correlative data can be reported at a later date.

SUMMARY

In an attempt to exploit the physiological properties of curare in the treatment of muscle spasm, a new preparation has been used. This preparation, *d*-tubocurarine in oil and wax, because of its slow absorption affords a much more satisfactory therapeutic index and a more prolonged effect than the aqueous solution. A series of cases in which patients with true muscle spasm were treated is described, and in addition a small group with a similar clinical picture but of possibly different origin is included.

CONCLUSIONS

1. "Muscle spasm" is often an integral part of the clinical picture of the acute low back syndrome.

2. Striking relief of symptoms in "low back" and similar syndromes may follow alleviation of muscle spasm.

3. A suspension of *d*-tubocurarine in oil and wax has proven very useful in breaking up the muscle spasm present in the conditions.

4. The difference in the response of patients exhibiting root compression from those with other types of disorders is described, and is suggested as a diagnostic test.

5. The use of *d*-tubocurarine in oil and wax for the prevention of deformity and alleviation of pain in early rheumatoid arthritis has led to promising results in a small group of patients.

6. On the basis of the clinical results so far obtained, it is believed that further exploration of this form of therapy is warranted.

The authors wish to express their obligation to the Attending Staff of the Columbia-Presbyterian Medical Center for the opportunity to study many of the cases presented in this series, and, in particular, to the late Dr. Clement B. Masson, whose unflagging interest and cooperation had much to do with making this work possible.

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Subacute Bacterial (Streptococcus Viridans) Endocarditis Treated with Penicillin*

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It has been only about three years since a patient with subacute bacterial endocarditis was an unfortunate object who had no hope, served no purpose other than to contribute his physical signs to the teaching of physical diagnosis, and finally his viscera to the study of gross and microscopic pathology. However, in this brief interim the use of penicillin has provided interest, animation, and, indeed, life itself to the majority of these individuals. There have been reports of a number of cures. Chief among these are the series of Dawson and Hunter,[1a] Loewe,[2] Loewe, Rosenblatt, Greene and Russell,[3] Bloomfield and Halpern,[4] Meads, Harris and Finland[5] and Bloomfield, Armstrong and Kirby.[6] Many other isolated cases and small groups of cases have also been recorded. Although the disease is not rare, it does not occur commonly enough to produce series involving large numbers of cases. Thus conclusions must be drawn from smaller multiple series, and it is therefore important that many reported series be carefully studied not only from the standpoint of the cures effected but also from the standpoint of failures encountered.

As in all diseases, early diagnosis and treatment are of paramount importance. Noteworthy in these and other published data is the unduly long period of time elapsing between the onset of symptoms, diagnosis and treatment. This period averaged fourteen and one-half weeks in this series. In spite of the high recovery rate, however, the occurrence and persistence of cardiac insufficiency following the infection and recovery gives the impression that this complication might have been obviated by earlier diagnosis and treatment. A presumptive diagnosis of subacute bacterial endocarditis should always be made in any patient having a heart murmur in conjunction with any one of the following: Chills, fever, emboli, splenomegaly, clubbed nails, hematuria or repeated pains in the back. A positive diagnosis may be made with a combination of the above plus the finding of Streptococcus viridans upon repeated blood cultures. Blood cultures should be taken twice or three times each day over a period of three or four days. This is important because it has been noted that positive cultures may be obtained either when the temperature is low or high. Cultures should be planted in blood agar plates and liquid media both aerobically and anaerobically, since different strains of Streptococcus viridans may be aerobes, anaerobes or facultative anaerobes. It is of exceptional interest to note that one of this series (no. 35749) was referred because of rheumatic heart disease with congestive heart failure, and although he at no time had any fever or leukocytosis, was found to have an enlarged spleen. This in conjunction with the heart murmur satisfied the requirements for a presumptive diagnosis of bacterial endocarditis. In all, nine blood cultures were

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made during three successive days. All were sterile except numbers 3, 5 and 9. These cultures showed from eleven to twenty-two colonies of Streptococcus viridans per cc. of blood. Obtaining blood cultures in this manner obviously will save time and add to the accuracy of the diagnosis. Early recognition and treatment might possibly obviate the occurrence of a fatal or crippling cerebral or other embolus and might indeed mean the difference between the success or failure of treatment.

This group of patients exhibited a clinical feature which has been outstanding in almost all patients with subacute bacterial (Streptococcus viridans) endocarditis which I have observed. In practically every instance these patients are perfectly willing to undergo any hardship in order to recover. I have never observed a patient with this disease who has not cooperated cheerfully and accepted any proposed treatment, from multiple needle punctures to artificial fever. This characteristic seems to be as typical in this disease as embolic phenomena or any of the other clinical or laboratory aspects. Bacterial endocarditis has not been proven where lack of cooperation, psychoneurotic tendencies and unwarranted complaining have been present in a suspected patient.

As yet there is little conclusive data as to the exact manner in which the lesions heal. Since there is practically no blood supply in the diseased valves, other than those involved by syphilis,[7] it seems only logical that the constant bathing of the vegetations by penicillin brings about healing by gradual penetration from the surface of the lesions. This would explain the necessity for prolongation of treatment until the vegetations have healed to their bases. The pathological findings in two patients who had healed subacute bacterial endocarditis lesions were reported by Rosenblatt and Loewe.[8] Healing with endothelialization of the diseased valves was noted. These patients died as the result of congestive cardiac failure several months after treatment. Cultures of the valves and adjacent myocardium were found sterile.

Congestive heart failure was a prominent cause of death in the majority of reports setting forth the mode of death, both before and since the advent of penicillin. It occurred in eight instances or 67 per cent of this series. In the eight of the eleven patients cured of their lesions but who died with congestive heart failure, seven or 88 per cent showed marked improvement from the standpoint of cardiac insufficiency after treatment with penicillin. Therefore, these findings indicate that one is not justified in presuming the ultimate disability to be so great as to warrant depriving any individual of treatment. Early and vigorous management of cardiac failure has probably contributed to the success of this series.

In vitro studies are important. It has been shown by Ellard Yow and his associates[10] that these laboratory procedures are a reliable guide in determining the type of antibiotic which is best suited for the bacterium involved. Unfortunately, some strains of Streptococcus viridans are not inhibited by penicillin, even in high concentration. In this series all strains of Streptococcus viridans were found to be sensitive to penicillin in a dilution of 1 unit per cc. These authors point out that blood levels higher than 0.1 unit per cc. are but very rarely obtainable. Subsequent *in vitro* studies have been conducted with penicillin dilutions of 1.0, 0.1 and 0.05 unit per cc. These more nearly approximate expected blood levels in patients.

From Table 1 it is learned that the total dosage of penicillin varied greatly, especially in those treated early in the series at which time there was no standard procedure, penicillin was available only in very limited quantities, and the dosage was often quite small. Indeed, there is no fixed

TABLE I

SUBACUTE STREPTOCOCCUS VIRIDANS ENDOCARDITIS*

Case Number...	25818	31234	35749	34932	City Hosp.	38396	39286	39748	38514	39242	43933	36529
Age	40	9	30	22	68	42	4	51	21	4	24	28
Sex	Male	Male	Male	Female	Female	Male	Female	Male	Female	Male	Female	Female
Basic lesion	Rheumatic mitral stenosis	Patent interventricular septum	Rheumatic mitral stenosis, aortic regurgitation	Mitral stenosis, rheumatic	Rheumatic mitral and aortic regurgitation	Rheumatic mitral stenosis, aortic regurgitation	Patent interventricular septum	Aortic stenosis, mitral stenosis, rheumatic	Patent ductus arteriosus	Patent ductus arteriosus and other congenital defects	Patent ductus arteriosus	Aortic insufficiency, mitral stenosis, rheumatic
Duration of illness before treatment.	7 weeks	4 months	Not known, no symptoms, palpable spleen only	4 weeks	5 weeks	5 months	2 months	7 months	6 months	6 weeks	4 months	3½ months
Infecting bacterium.	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans	Streptococcus viridans
Complications...	None	Pulmonary infarcts, cardiac insufficiency	Cardiac insufficiency	Endocarditis began 10 days after normal delivery	Cardiac insufficiency	Cardiac insufficiency	None	Duodenal ulcer, cardiac insufficiency	Pulmonary infarctions, mild cardiac insufficiency	Cardiac insufficiency, pericardial effusion	Pulmonary infarctions mild cardiac, insufficiency	Congestive failure, ruptured aortic cusps mycotic aneurysms
Embolic phenomena.	Generalized small	Lungs, spleen and generalized	Spleen, kidneys, finger tips	Multiple petechiae in skin	None	Spleen, kidneys, generalized	None	Spleen, kidneys	Spleen, kidneys, fingers	Kidneys, spleen, generalized	Lungs, spleen kidneys, generalized	Multiple at outset none after cultures negative and temp. normal
In vitro studies...	Inhibited by penicillin not by sulfonamides	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Inhibited by penicillin	Cultures obtained elsewhere	Inhibited by penicillin	Cultures obtained elsewhere	Inhibited by penicillin at outset, but later only in concentration greater than 1 u. per cc.	Inhibited by penicillin	Inhibited by penicillin not by sulfonamides
Treatment	Penicillin 5,000,000 units 21 days, I.M.	Penicillin (a) 2,030,000 units 20 days. (b) 2,000,000 units 20 days. I.M. drip	Penicillin 3,150,000 units 14 days, I.M.	Penicillin 3,335,000 units 21 days, I.M.	Penicillin 5,200,000 units 22 days	Penicillin 4,000,000 units 20 days I.M.	Penicillin 4,885,000 units 42 days, I.M.	Penicillin 3,520,000 units 15 days, I.M.	Penicillin (a) 400,000 units 4 days. (b) 600,000 units 6 days. (c) 1,000,000 units 10 days. (d) 2,000,000 units 20 days. (e) 4,200,000 units 21 days. Total 8,200,000 units 61 days	Penicillin 6,980,000 units 43 days. Para-aminohippuric acid 8 days	Penicillin (a) 600,000 units 6 days. (b) 2,000,000 units 20 days. (c) 2,000,000 units 20 days. (d) 5,000,000 units 21 days. Total 9,600,000 units 67 days	Penicillin 6,250,000 units 25 days
Sequellae	None	None	None	None	None	None	None	Subdeltoid bursitis	Excision of ductus arteriosus	Congestive heart failure	Excision of ductus arteriosus	
Blood cultures sterile	24 hours	24 hours	12 hours	4 days	12 hours	12 hours	24 hours	12 hours	24 hours	42 days	24 hours	24 hours
Cause of death	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	Cardiac failure bacterial lesions healed
Result follow-up	Cure 24 months	Cure—no cardiac insufficiency 22 months	Cure—slight cardiac insufficiency 19 months	Cure 19 months	Cure—cardiac failure markedly improved. 17 months	Cure—no cardiac insufficiency. 16 months	Cure 15 months	Cure 15 months	Cure 14 months	Cured—definite cardiac failure, cultures sterile. 13 months	Cure—murmurs and thrill cone. 12 months	Died—10 weeks after cultures sterile

* Recapitulation of twelve cases of subacute bacterial (Streptococcus viridans) endocarditis.

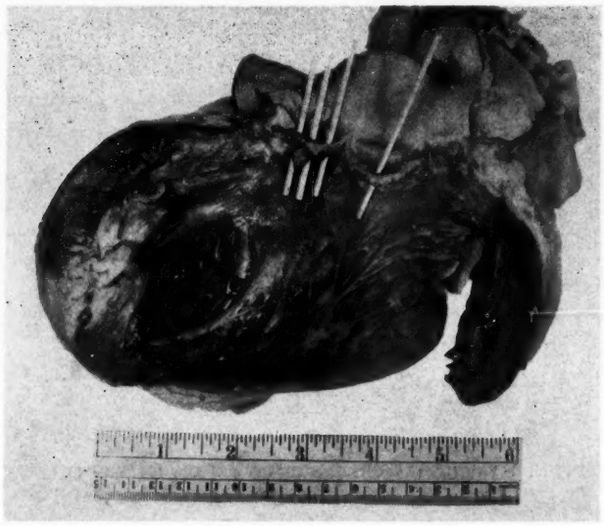

FIG. 1. The margins of the aortic cusps are rolled and thickened. The surfaces are glistening and free of vegetations or other active inflammatory changes. Probes are in place through the four perforations of the valve cusps. These perforations resulted from mycotic aneurysm formation. Marked hypertrophy and dilatation of the left ventricle are evident.

standard procedure today. There seems to be general agreement, nevertheless, that a minimum treatment period of six to eight weeks, employing a daily dosage of 250,000 units of penicillin is desirable. When one considers the deep seated implantation of the bacteria in the vegetations, the advisability of prolonged treatment becomes obvious. The failure of sulfonamides and other bacteriostatic agents to penetrate these lesions in many cases probably has accounted for their failure in most instances. Meads[9] has pointed out the urgency of giving adequate dosages of penicillin in any type of infection which might be susceptible to this agent. Therefore, the total daily dosage should be increased in the event of continued positive blood cultures or fever, and the time interval shortened as the case demands.

Other matters of importance are blood transfusions, adequate nutrition, general hygienic care, and, when practicable, the elimination of focal Streptococcus viridans infection. This type of infection has been found principally about the teeth and gums, and is best managed while the patient is still maintained on a full blood concentration of penicillin. If gingivitis of appreciable degree exists along with dental caries, extensive dental extractions should be performed. This has resulted in negative blood cultures in one patient who previously had exhibited occasional positive cultures during the course of her therapy.

The following series (Table 1) embraces twelve cases of proven subacute (Streptococcus viridans) endocarditis treated with penicillin. All have been followed for from twelve to twenty-four months. Of these eleven (or 92 per cent) are still alive and well. A number of patients have been treated since but have not been observed over a sufficient period of time to warrant reporting at this time. Heparin or other anticoagulants were not employed in any of these cases.

One patient (34932) developed a recurrence of her Streptococcus viridans infection and the classical picture of subacute

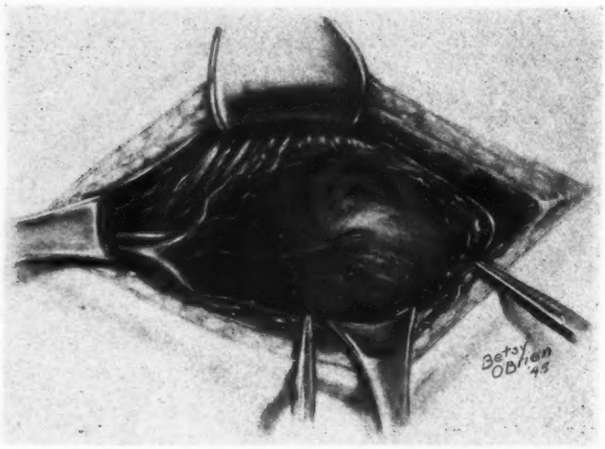

FIG. 2. Drawing at operation of the mycotic aneurysm of the right popliteal artery.

bacterial endocarditis with multiple emboli. The organisms recovered in blood cultures were found to be sensitive to penicillin *in vitro*, and penicillin therapy resulted rapidly in a good clinical response and negative blood cultures. She was free of fever and clinically well three months after treatment of the second infection.

An autopsy was performed on one of the twelve who expired (36529) and death was found to be due to congestive cardiac failure and pneumonitis. At the time of her original admission she showed frank evidence of perforation of the aortic valve in the form of a grade V or VI "base violin string type" of diastolic murmur along the entire sternum and an accompanying pronounced diastolic thrill. As noted in Table I, the cultures were free of Streptococcus viridans within twenty-four hours after penicillin was instituted, and they remained so for ten weeks. Furthermore, the sedimentation rate was normal. The added factor of cardiac failure brought about by left ventricular strain as the result of the multiple perforations in the aortic cusps was the most direct cause of death. Pathologic findings showed chronic mitral and aortic rheumatic valvular disease with no evidences of remaining Streptococcus viridans infection. The perforations in the aortic valve are illustrated in Figure 1. A further interesting complication was a mycotic aneurysm of the right popliteal artery, which was excised after penicillin therapy was started. (Fig. 2.)

DISCUSSION

Twelve patients with subacute bacterial (Streptococcus viridans) endocarditis which have been treated with penicillin are presented. Eleven (or 92 per cent) are alive and well from twelve to twenty-four months after treatment. Pertinent data are summarized in Table I. Anticoagulants were not employed.

The success of the treatment of subacute bacterial endocarditis lies first in early diagnosis, which is hastened and confirmed by obtaining blood cultures three times daily for three successive days; second, in prolonged treatment with penicillin in adequate dosage; third, management of the cardiac failure; fourth, employment of general measures, especially blood transfusions and replacement of serum proteins; and fifth, in the use of *in vitro* studies which are of inestimable value in prognosis and in governing the course of therapy.

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Folic Acid and the Bone Marrow in Radiation Therapy*

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FROM October, 1942, to July, 1946, 191 cases of lymphoblastomas were observed. This group included giant follicular lymphoblastoma, lymphosarcoma, reticulum cell sarcoma and Hodgkin's disease. The bone marrow studies revealed in all instances a marked depression of the myelopoietic and erythropoietic systems. The normal myeloid-erythroid ratio varied between 2:1 and 8:1 and the myeloid-lymphoid ratio 5:1. It was noted that the decrease in the myeloid-erythroid elements was of a depressed type with the ratios more or less constantly maintained, whereas the myeloid-lymphoid ratios were almost completely reversed, i.e., 0.5:5. These features were observed consistently when the bone marrow was studied on admission. It was assumed that these effects were due primarily to the overactivity of the reticulo-endothelial system in these diseases. These bone marrow effects were reflected in the peripheral blood by a marked anemia and neutropenia with an increase in the lymphocytic elements. In the lymphoblastomas this cytophagic and hormonal (?) depressant effect on the bone marrow would seem to be rather comparable to the depressant effects seen on these structures in primary splenic neutropenia, thrombocytopenia, splenic pancytopenia and Felty's syndrome.

When radiation therapy was introduced in the treatment, the anemia and neutropenia became progressively more severe necessitating on the average daily to weekly transfusions of red cells or whole blood in order to maintain, as closely as possible, the red cell, hemoglobin and neutrophilic levels within normal limits. These depressant and destructive effects on the bone marrow elements are believed to be due to a combination of the excessive cytophagic activity of the reticulo-endothelial system in these diseases and the destructive effects of radiation.

There were 122 cases given routine radiation therapy accompanied by transfusions. In all of these cases the average length of hospitalization was nine and eight-tenths months with a range from five to thirteen months. The radiation reactions and the general depressant effects were severe. The bone marrow and peripheral blood remained continually abnormal. The sedimentation rates decreased slowly but never returned to normal. The stress on blood bank, donors, laboratory and hospital personnel consequent to maintaining a semblance of hematologic equilibrium in these patients during radiation therapy was profound. These factors were so formidable that an adjunct to this therapy was sought. Beginning January, 1944, the Lederle Laboratories, through the courtesy of Doctor Thomas Jukes, supplied liberal quantities of folic acid. This was supplied in bulk powder and in capsule form so that large dosages could be given routinely ranging from 75 to 150 mg. three times daily. Considerable counsel and aid was given by Dr. Daft and Dr. Sebrell of the National Institute of Health, Washington, D. C.

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There were seventeen patients treated with large doses of folic acid without any other therapy. There was no demonstrable beneficial influence on the course of the disease. Subsequently these cases were given radiation therapy.

There were sixty-nine patients treated with radiation therapy, transfusions and folic acid. When folic acid was added to radiation therapy, it was noted that the patients withstood radiation therapy better, with less nausea, vomiting and general depressing physical effects. The sedimentation rates returned less slowly to normal. The necessity for red cell or whole blood transfusions decreased in frequency to an average of one in eighteen days. The average time of hospitalization was reduced from nine and eight-tenths months to five and three-tenths months with a range from three to six months. The bone marrow on discharge showed an increase in the myeloid and erythroid elements and the myeloid-lymphoid ratios tended to return to normal although they never reached normal.

SUMMARY

There were 122 patients with lymphoblastoma treated with radiation therapy and transfusions. The depressant effect on the bone marrow by the disease and therapy was profound.

Seventeen patients were treated with folic acid alone without any demonstrable effect on the course of the disease.

Sixty-nine patients were treated with folic acid in addition to routine therapy. The addition of folic acid seemed to decrease the deleterious and depressant effects of radiation therapy on the bone marrow, decrease the necessity for as frequent transfusions, shorten the period of hospitalization and seemed to have some beneficial influence on the course of the disease during radiation therapy.

CONCLUSION

Folic acid is recommended as a useful adjuvant in maintaining the hematologic well-being of patients receiving massive and prolonged radiation therapy.

Clinical Vibrometer*

An Apparatus to Measure Vibratory Sense Quantitatively

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THE clinical signs of peripheral neuropathy result from an interruption in the transmission of impulses in both sensory and motor fibers. The more common sensory stimuli used for detecting the existence of a neuropathy consist of those necessary to elicit pain, touch, sensation of heat and cold, and vibration sense. It is well known that the more profound the disease, the greater the stimulus necessary to elicit a response in any of these sensations. Thus it would appear that any method which could quantitatively measure the threshold of the response to a stimulus would serve as a more satisfactory criterion for clinically evaluating the intensity of disease than if one were compelled to resort to conclusions based upon crude clinical perceptions.

FIG. 1. Clinical vibrometer in use.

It appears that one of the earliest functions to be disturbed in peripheral neuritis is that of vibration sense. The determination of impairment in vibratory sense may, therefore, serve as a function of impairment in the transmission of other impulses. In order to estimate quantitatively the degree of impairment in vibratory sense, one may use a vibrating instrument in which either the frequency of vibration or the amplitude of vibration can be altered.[1,2]

We have devised a simple apparatus for estimating degrees of impairment in vibration sense by electrically activating a tuning fork which has the property of varying the amplitude of vibration while keeping the frequency constant.

This apparatus consists of a tuning fork, carrying an electromagnet on one tine, the other tine serving as the pole piece. The electromagnet is energized by a current

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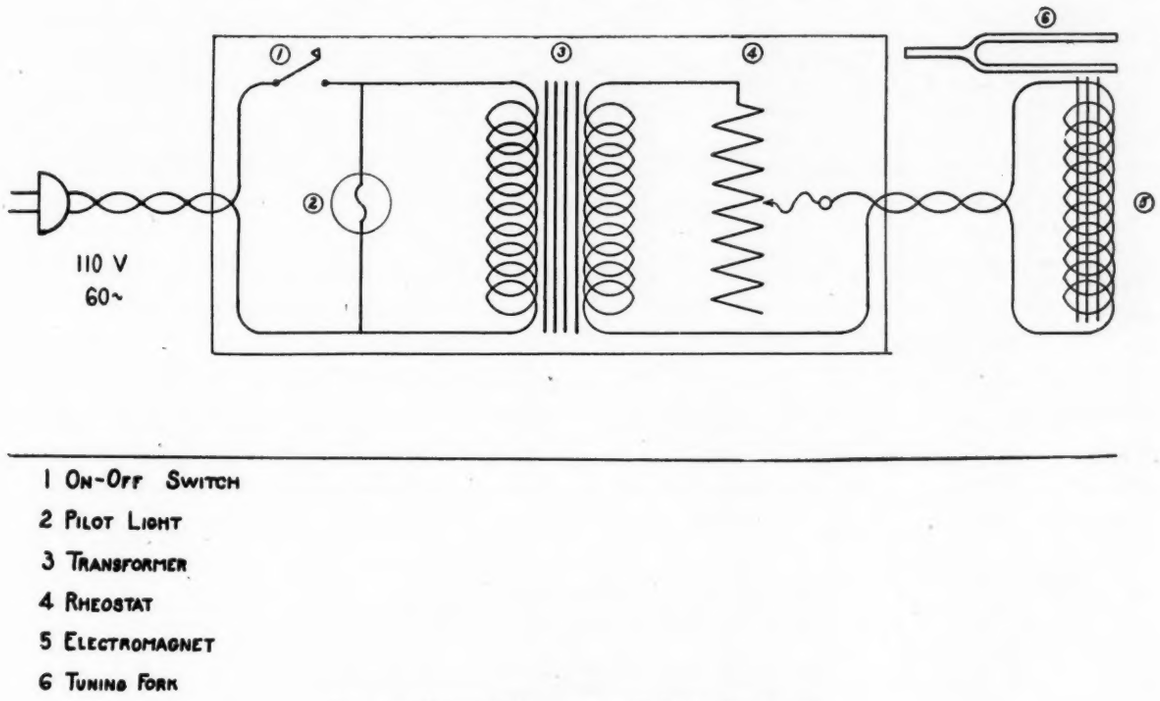

Fig. 2. Wiring diagram for clinical vibrometer.

obtained from a 60 cycle power line. The usual 110 volt current is reduced through a transformer to 6 volts. The intensity of the current is controlled by a wire-wound rheostat. The amplitude of vibration is controlled by the rheostat which has a calibrated circular dial. The calibrations are in arbitrary units from 100 to 0, which permit duplication of any desired setting. (Fig. 1.) The wiring diagram is seen in Figure 2.

Rotating the indicator from 100 to 0, reduces the resistance in the rheostat, thus allowing for a greater amplitude of vibration in the tuning fork. We arbitrarily set the scale so that when the indicator was at 100, the amplitude of vibration was so minimal that the normal subject could just barely detect it.

We found that the normal subject was thus just able to detect vibrations produced with the resistance dial set at 90 or more, up to 100. We also found that patients who had an impairment in vibratory sense, responded to those higher amplitudes of vibration when the resistance dial was below 90. There appeared to be a direct relationship between the degree of impairment in vibratory sense and the amplitude of vibration to which the patient responded. Thus as vibratory sense was found to be more impaired, responses were initially perceived only to such high amplitudes as were detected by the lower figures on the dial.

CONCLUSION

An apparatus is described for quantitatively measuring vibration sense.

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Impaired Vibratory Sense in Diabetes*

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PERIPHERAL neuritis is one of the most common complications of diabetes. In spite of its clinical importance, no procedure employed in the traditional neurological examination has offered the physician an opportunity to obtain a satisfactory concept of the intensity of involvement of the peripheral nerve. The vibrometer which we have described in the previous article makes it possible to quantitate the intensity of the neuropathic state. This is predicated upon the assumption that impairment in vibratory sense is a function of impairment in the transmission of other sensory impulses in the involved peripheral nerve.

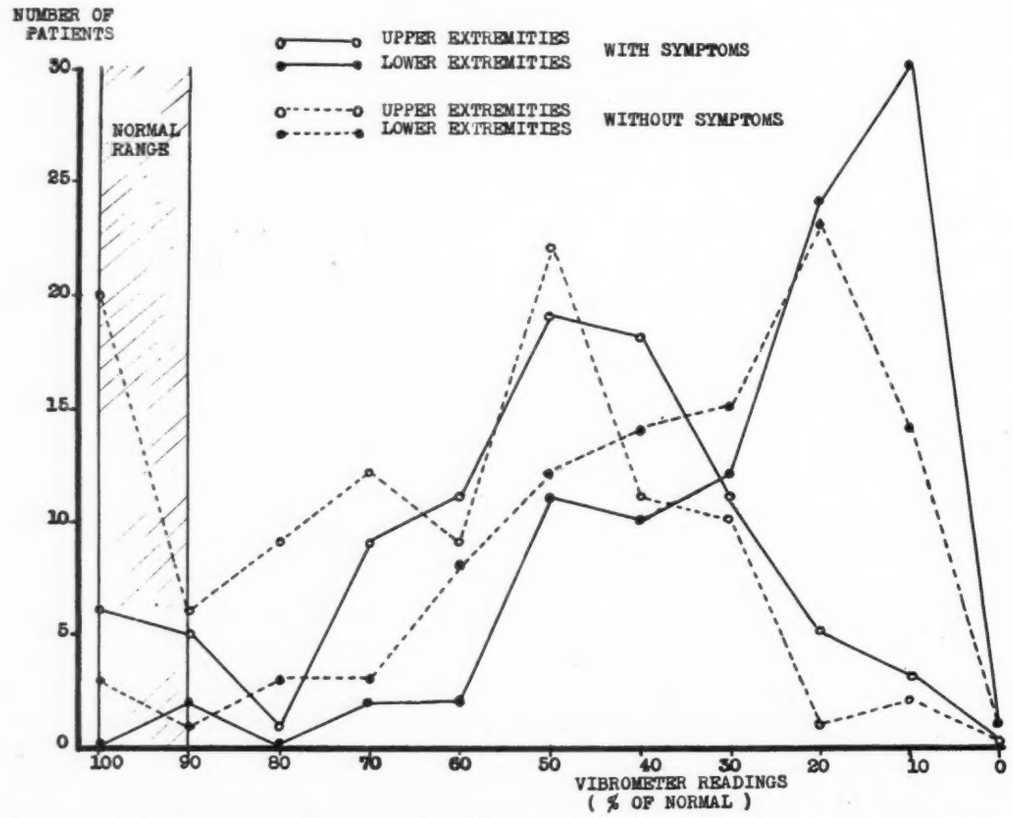

FIG. 1. Graph showing impairment in vibration sense in diabetes. Solid line represents patients with symptoms of peripheral neuritis. Broken line shows the patients without neuritic symptoms. Shaded area shows the normal zone. Shift in curve to right indicates an increasing number of patients showing more profound impairment in vibration sense. Note that the lower extremities are more severely involved in most of the cases than the upper extremities. Note also that the curve of patients without neuritic symptoms almost parallels the curve of cases with symptoms of neuritis.

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Recognizing that peripheral neuritis in diabetes assumes, generally, a stocking and glove distribution in the extremities without revealing any involvement according to somatic segmental levels, our plan of study consisted in testing the tips of the digits in the cases under observation. After observing that all the digits of the same limb gave approximately the same readings, it was decided, for purposes of simplicity, to record the readings on the tips of the index fingers of the upper extremities and of the large toes of the lower extremities.

This study is concerned with a determination of the threshold of vibratory sense in diabetics. Having once established the threshold of response with our instrument in 100 normal unselected individuals, we had a standard by means of which we could be guided in quantitating impairment in vibratory sense in diabetics. The first part of our study consisted in establishing these thresholds in 100 diabetics who presented classical neuropathic symptoms in the extremities consisting of one or more of the following: numbness, burning sensations, sticking pains, sensations of pins and needles, cramp-like pains, stiffness and formication. The second part of the study consisted in quantitating vibration sense in 100 diabetics who had no symptoms of neuritis. The accompanying figure (Fig. 1) is a graphic summary of these 200 cases. The ordinate is calibrated in terms of number of patients and is plotted against the vibrometer reading in the abscissa. It will be seen that in those with peripheral neuritis, there was not a single patient who revealed the existence of normal vibratory sense in the lower extremities and only two out of 100 showed normal readings in the upper extremities. It will also be observed that the majority of the cases had a much more profound impairment in vibratory sense in the lower than in the upper extremities.

TABLE 1

No.	Age	Sex	Duration of Diabetes	Daily Insulin Dose—Units	Symptoms of Neuritis	Vibrometer Readings	
						Upper	Lower
1	13	M	2 yr.	53	None	100	70
2	16	M	3 yr.	60	None	60	30
3	18	F	9 mo.	78	None	80	60
4	13	M	3 yr.	57	None	70	60
5	19	M	6 yr.	95	None	90	70
6	12	M	7 mo.	65	None	100	100
7	11	M	1 mo.	15	None	100	90
8	10	M	2 mo.	25	None	100	40
9	23	M	9 yr.	130	None	100	100
10	17	M	11 yr,	35	None	100	60
11	8	F	2½ yr.	70	None	100	100
12	20	F	4 yr.	80	None	70	40
13	19	M	7 yr.	60	None	100	90
14	24	M	2 yr.	56	None	80	80
15	16	F	9 mo.	23	None	100	100
16	14	M	5 yr.	90	None	100	80
17	21	M	5 yr.	70	None	90	70
18	18	F	8 yr.	135	None	100	100
19	8	M	3 yr.	35	None	100	100
20	12	F	6 yr.	50	None	80	80
21	22	F	7 yr.	75	None	100	80
22	14	F	1½ yr.	42	None	100	100
23	23	M	7 yr.	90	None	90	70
24	7½	F	1½ yr.	60	None	100	100
25	12	M	6 yr.	80	None	100	100
26	13	M	1 yr.	55	None	100	100
27	16	F	4 yr.	65	None	70	50
28	21	M	4 yr.	72	None	100	50
29	8½	F	2 yr.	42	None	100	100
30	9	F	2½ yr.	128	None	100	100
31	14	M	9 yr.	72	None	100	60
32	16	M	3 yr.	100	None	100	80
33	17	F	2 yr.	100	None	100	100
34	17	M	5 yr.	35	None	100	50
35	6	F	1½ yr.	35	None	100	100
36	19	F	1 yr.	60	None	100	100
37	22	M	8 yr.	100	None	100	100
38	20	F	8 yr.	112	None	100	100
39	14	F	9½ yr.	74	None	100	100
40	22	M	3 yr.	55	None	100	80
41	17	M	4 yr.	144	None	100	100
42	7	M	3 yr.	50	None	100	100
43	16	M	11 yr.	90	None	100	100
44	25	F	9 yr.	36	None	80	50
45	20	M	16 yr.	112	None	100	80
46	24	F	22 yr.	68	None	100	100
47	15	M	2 yr.	53	None	100	100
48	19	F	9 yr.	112	None	100	100
49	22	F	5 yr.	60	None	100	70
50	23	M	3 yr.	95	None	100	70
51	17	F	6 yr.	85	None	100	100
52	13	F	2 yr.	52	None	100	100
53	13	M	2 yr.	60	None	100	100
54	20	F	2½ yr.	68	None	100	100
55	25	F	13 yr.	56	None	100	100
56	11	F	7 yr.	44	None	100	100
57	20	F	13 yr.	96	None	100	70
58	23	M	18 yr.	64	None	100	100

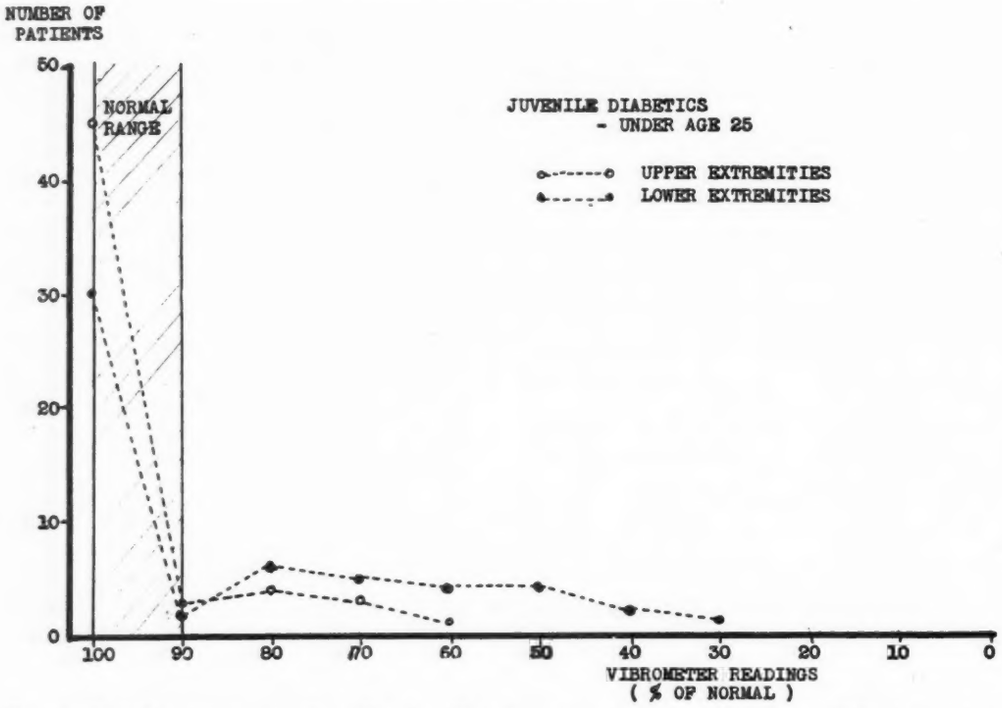

FIG. 2. Graphic summary of studies in vibration sense in fifty-eight young diabetics under twenty-five years of age. Note the small incidence of impaired vibratory sense and the mildness of the impairment.

What has proved to be most significant from this study is that diabetics who had no symptoms of neuritis whatever revealed an impairment in vibratory sense. It will be seen from the chart that only twenty-six out of 100 patients without symptoms gave normal readings for vibratory sense in the upper extremities and only four out of 100 had normal readings in the lower extremities. The remainder showed a specific impairment in vibratory sense. It is striking that the intensity of impairment in these cases is almost as great as in the diabetics with symptoms of neuritis.

It is apparent from this study that this method for testing vibratory sense has made it possible to detect the existence of a subclinical neuropathic state in diabetics who do not have symptoms of neuritis.

We then conducted a study of fifty-eight juvenile diabetics under the age of twenty-five. There are several pertinent observations in this group which, on analysis, appear to be provocative and have upset some traditional concepts with regard to the rôle of the control of diabetes in relationship to the development of neuropathic states.

In Table 1 will be found a summary of these cases and in Figure 2 will be seen a graphic chart in which the number of cases is plotted against intensity of impairment in vibratory sense. The following conclusions can be deduced from these observations: First, there was not a single case who had symptoms of neuritis under the age of twenty-five; and second, the subclinical neuropathic state was found to exist in 14 per cent of the cases in the upper extremities and 43 per cent of the cases in the lower extremities. All the patients under the age of ten had entirely normal readings. There were six cases in this group. No patients had impairment in vibratory sense in the upper extremities of an intensity greater than 60 per cent of the normal and in the lower extremities greater than 30 per cent

of the normal. This would indicate that age plays a part in predetermining the development of neuropathy only past the age twenty-five.

What is most disturbing in the observations made in the juvenile group is that there does not appear to be any relation between the duration of the diabetes, the intensity of the diabetes, or the degree of control of the diabetes, and the intensity of impairment of vibratory sense. We can at this point cite the case of a female who developed her diabetes at two years of age. (Table 1, Case 46.) She is now twenty-four years old and reveals normal vibratory sense readings at this date in spite of the fact that she is a severe diabetic and is satisfactorily maintained on a high carbohydrate diet with 68 units of insulin per day. On the other hand, this patient can be compared with another juvenile in whom diabetes was known to exist for only two months and vibratory sense studies revealed 40 per cent of normal in the lower extremities. (Table 1, Case 8.) This child has proved to be a mild diabetic, is fully controlled and free from glycosuria, is thriving, and the total insulin requirement is 25 units per day.

We should like also to cite the severe case of a juvenile diabetic in whom the severity of the disease can be recognized by his insulin requirements which consist of 130 units per day. (Table 1, Case 9.) His vibratory sense readings are entirely normal. It is interesting to mention in connection with this case that he has been diabetic for nine years and is seldom sugar-free.

Then there is also the case of a severe diabetic who has never been particularly cooperative and in whom persistent glycosuria and hyperglycemia have been characteristic features in spite of the fact that he has taken an average of 112 units of insulin per day. (Table 1, Case 48.) He has had diabetes for nine years and his vibratory sense readings are normal. These observations have a tendency to upset our traditional concepts that adequate control of diabetes can protect the patient against the development of neuropathic states.

There is evidence that this phenomenon of impaired vibratory sense in the diabetic is reversible. This will appear in a paper on the treatment of peripheral neuropathies in the diabetic in the Proceedings of the American Diabetes Association.

CONCLUSIONS

1. Peripheral neuropathic states can exist in the diabetic in subclinical form and can be recognized by quantitative studies of vibratory sense.

2. In diabetics with peripheral neuritis, 90 per cent had impairment in vibratory sense in the upper extremities while 98 per cent had impairment in the lower extremities.

3. Impairment in vibratory sense occurs almost as frequently and almost as severely in diabetics without symptoms of neuritis as it does in those with symptoms.

4. No diabetic under the age of ten had any impairment in vibratory sense.

5. It appears from these studies that not only impaired vibratory sense but also symptoms of neuritis can develop in the diabetic regardless of the duration of the disease, the severity of the disease or the degree of control of the disease.

The Planning of a Camp for Diabetic Children

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In the consideration of the problem of a summer camp for diabetic children, a problem which is growing and will increase as time goes on, it is believed that it is timely to bring forth the needs and the essential outlay of such a camp. It seemed unfortunate that all the advantages of a camp life had been denied to the diabetic child whose very life depended upon special medical care, restricted diet and the insulin syringe. Cognizant of this, I established a summer camp in 1929 near Cleveland for diabetic children.

The reasons were many. After the discovery of insulin, diabetic children were kept alive. They no longer presented the pitiful picture of slow starvation until death released them. But just keeping a child alive was no longer sufficient. A chance for his normal growth and development was essential. His life would have to parallel in all aspects that of normal children.

The diabetic child needs the advantage of a healthful vacation even more than does a normal child, for his daily routine is an onerous thing. The diabetic child needs the exercise which helps to metabolize his food intake. It has been discovered that exercise helps partly to replace the insulin up to a certain point, for insulin dosage can often be reduced considerably while a child is at camp.

More than other children, he is apt to be introspective and inclined to be a psychological problem. The very nature of his disease is the cause for this, as well as doting parents or unintelligent handling. By communal living with many other children, diabetics like himself, he can realize for the first time that he is not alone with his problems. He has the advantage of seeing how others face theirs and solve them in healthy, normal ways.

The well controlled diabetic presents the most helpful and encouraging material with which to work. The majority of diabetic children have IQ's well in advance of normal children of the same age. By giving them the advantage of a normal outlet for their energies and initiative, their growth into responsible citizenship is assured.

Lastly, by providing a place of vacation for the diabetic child, the mother is relieved of her arduous task for a brief period in which she, too, can gain some rest and renewed strength to face the burden of the child's care when he returns home.

In the past eighteen years of Camp Ho Mita Koda's* existence, these ideas have proven beyond question its worth to the community and its invaluable service to the diabetic children. Because this camp has been the pioneer in this field, many questions have come to my desk concerning its nature and organization. In order to help others who might be interested in establishing like facilities for diabetic children, I herewith state my reasons for arriving at the present type of set-up, outlining briefly its physical aspect as well as its staff requirements.

* Ho Mita Koda is Sioux Indian and means "Welcome my friend."

CAMP SITE

The camp site is the first consideration. Should it be a separate camp, devoted just to the needs of diabetic children, or should such a camp be a small unit inserted into a general camp already existing?

There are advantages and disadvantages in both. A camp for diabetic children is a highly specialized camp, serving the needs of children as other camps do in addition to serving their medical needs. This latter presents no small item. If incorporated into a general camp, it has the advantage of a large group of children in its general program. The great disadvantage is that the diabetic child is constantly pointed out as such when little incidents occur, such as insulin reactions, the necessity of eating at a separate table, the need of laboratory work, etc. Thus the focus is on the diabetic child. This is automatically eliminated when such a child is in a camp solely for diabetics where all problems are alike. Such an association then in a general camp creates certain psychologic problems or reactions which are not desirable. It does not spare the child.

Another factor in a general camp is the maintenance of a corner in the kitchen to care for the diabetic diets. One will find in such a large kitchen more people, more confusion, more friction than when such a kitchen serves only the needs of diabetic children. It is a big load at best and should, therefore, not be made any heavier.

Thus, on the whole, I believe that it is much simpler, much more efficient, if the camp is devoted entirely to the needs of the diabetic.

THE PHYSICAL PLANT

The physical plant had to fill the following needs: (1) A central unit for all community activities; (2) sleeping quarters for campers; boys, girls; and the staff: men, women; (3) toilet as well as bath facilities for the same.

THE CENTRAL PLANT

Main Hall. The Great Hall is the largest room in the main hall. Its focal point is a huge fireplace around which much of the program is built. The stage opens onto this room. Here children gather for talks, movies, plays and general discussions; here an occasional dance is held as well as radio programs. On rainy days, especially in the evenings, it is the chief center of activities.

Library. We realized that a library was needed in the camp. For lack of space we combined this room with the stage so that it serves a dual purpose. Here around an open fireplace is housed good literature for all age groups. The floor of the room is a foot and a half higher than in the main hall, with a wide opening to frame it as a stage when used for that purpose. It is a much needed and useful room in the planning of camp programs at night. Much stimulation can be induced for further individual initiative. Short sketches and skits, often spontaneous by the campers, are encouraged. It is stimulating as well as entertaining. The little ones try to imitate the older ones and to outdo them.

Dining Room. I have utilized a large screen porch on the main building, some 110 feet long, for dining purposes. This frees the main hall of unnecessary confusion and is much more enjoyable for it is almost out of doors. The children while eating, look out on the green lawn and trees, the fountain and the totem poles. It was essential of course that the porch be screened. While on the problem of screening, I might suggest one point: use copper screen throughout the camp. It is the greatest economy by far in the long run. All screen doors are reinforced with heavier mesh screening below where children's knees or feet have a way of opening them.

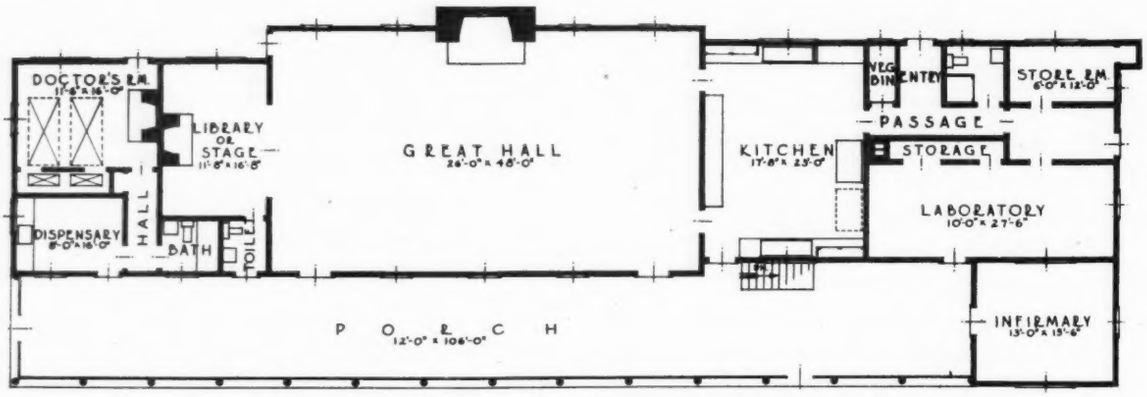

FIG. 1. Plan of main building for summer camp for diabetic children.

Kitchen. The kitchen in a diabetic camp is a very important and specialized unit. A graduate dietitian is in charge. She does all the planning, buying, measuring and supervising of all the details. Her task is easy in a general camp where the main issue is to provide good and tasty food and plenty of it. In a camp for diabetics, each individual child is on a planned diet which has to be calculated and weighed for each meal. The planning is done by the dietitian the night before in cooperation with the medical director. It is impossible in a camp of fifty to sixty children to prescribe fifty to sixty different diets, many of which would vary from each other by only a few Gm. It would be a useless waste of time. Thus diets can be grouped into about five or six routines in order to eliminate confusion. Each such diet, as a further check on its accuracy, is served on special colored plates; thus let us say, a 1,600 calorie diet is served on red plates, a 2,000 calorie diet on green plates, an 1,800 calorie diet on yellow plates, etc. This eliminates mistakes, for a child knows whether he is to get the yellow, the red or the green plates and if a wrong tray is offered him, he will immediately call attention to the fact.

A good cook under the supervision of the dietitian takes care of preparation of the food so that it is attractive, appetizing and of good nutritional value. The dietitian and her helpers, girls who are recruited from among the older group of campers, serving a week or two at a time as a part of their training, measure the diet according to the outline planned by the dietitian. This assures rapid service and the food is palatable from the standpoint of its warmth.

Dish washing is done in a similar manner as in hotels. The dishes are rinsed in a unit of boiling water after preliminary washing and lifted from it in racks and allowed to air dry. The wiping of dishes is against a state law, and is thus eliminated in all camps.

Refrigeration is a large item. Food for seventy to ninety people, campers and staff, takes much space. Ice refrigeration for some foods is adequate. In addition an electric refrigerator is helpful, especially when a unit has to be opened at more frequent intervals.

A small cellar under the porch is a very useful item as much of the food can be taken care of in such a cool place, for the volume of vegetables, fruits, etc., is enormous.

Hot and cold running water is provided for the kitchen by a separate heating plant attached to the main building in which the kitchen is located. Also a large screened storage room and smaller bins are needed for vegetables, fruits and staples.

The disposition of the garbage may require a disposal unit unless one can arrange with some near-by farmer to haul

the garbage away daily. I have been fortunate to make such arrangements at my camp by agreeing to keep all paper and inedible objects separate. A small, screened unit for the garbage cans is essential a short distance from the main hall.

Infirmary. In an institution dealing with medical problems, the infirmary is a very necessary part of the set-up. Anything can happen in a camp. An infirmary meets the needs in all emergencies such as reactions, acidosis, isolation, etc. It is especially useful at night, for by removing a sick camper from the general sleeping quarters, the rest of the children are not disturbed. The infirmary and laboratory, too, are the headquarters for the night nurse. The infirmary is next to the laboratory where any needed test can be performed.

Laboratory. The laboratory is an essential part of the camp. Urine examinations, blood sugar estimations and other special tests, when indicated, are performed here. It also serves as the center of medical activity. For that reason it requires a fairly large room. The work is done by the staff consisting of a resident physician and nurses. In fact, regarding the urine examinations for instance, the question is often asked: Do the children do the urine analyses? The answer is "no." They come to camp not to be burdened with medical care of themselves. Furthermore, they do not come for instruction. That is the field of the family physician and it is not encroached upon. The camp is responsible for the medical care of the children while they are there; after that it turns them back to the family physician for his continued care and management.

We have a telephone with extensions in all vital sections of the camp.

Sleeping Quarters. Sleeping quarters are planned on the basis of the needs of this special group and on surroundings. We built units for eight to ten children. These are open screened buildings, size 24 by 56 feet, giving ample room for cots and lockers and bedside tables. The units for girls are at some distance from those of the boys to insure privacy. In each unit children are grouped according to age. The roofs of all the buildings are insulated with celotex under the shingles which adds much to comfort during the hot summer. This point is quite essential to bear in mind.

Sleeping quarters for the staff were created in similar or in smaller units. A few small buildings accommodate husbands and wives. We have found that often young couples make good staff members. Sleeping quarters for the help, cook, assistant cook, handy man, etc., required separate small units. The quarters for the night nurse are at some distance from the general camp outlay to insure her undisturbed rest and sleep during the day.

One must bear in mind that these children require supervision at night. The night nurse must make rounds every half hour until midnight, then every hour during the rest of the night. She has to observe each sleeping cabin to see if all is well, checking to see if there are any insulin reactions during sleep. For that reason the buildings should not be too far apart. There are rainy nights. A camp on a rainy night with three to five reactions in separate buildings can present a terrific problem. Fortunately, since protamine zinc insulin came into use, this phase of the problem has been much reduced. It once was the major problem at the camp.

Toilet and Bath Facilities. It is cheaper to plan for all bathing and toilet facilities in one general building, the bathhouse, than in many separate buildings. Here again we had to provide for separate needs of campers, boys and girls; and staff, men and women. Our bathhouse is divided into four separate sections by complete partitions, each one to take care of the needs of each

of the four groups. Each room has its separate entrance from the outside and is broken down into space for toilets and another space for showers and wash stands. Hot showers, running hot and cold water and flush type toilets are provided in each of the four subdivisions. The heating unit is in the center part of the building. A septic tank provides for sewage disposal.

Water Supply. As camps are located far from the city, one has to provide for water supply. I solved this problem by drilling a well 132 feet deep, installing a deep well electric pump and a 5,000 gallon pressure storage tank underground. This has taken care of our needs adequately and efficiently.

Sewage Disposal. Sewage disposal had to be provided for the entire camp. As all the baths and toilets are housed in just two buildings, the bathhouse and the main hall, the problem was simplified. We built a large septic tank. The discharge from it, clear, unpolluted water, is lead underground to a convenient distance from the camp where it can empty into a running creek. In the kitchen, we did not forget the fat traps, as otherwise the sewage would be plugged up. Sanitary engineers helped here as state laws had to be complied with. At the close of camp each season, all water has to be drained to prevent the pipes from freezing.

Lighting. Electricity for all buildings is the safest means of lighting. It is needed also for the pump, the craft shop, etc. We were fortunate in having electricity wired into the camp. A Delco unit would have had to be installed if a utility line had not been available.

CRAFT SHOP

The craft shop is a separate building used for various activities. It is a place especially busy on rainy days. If properly conducted, it can do much for the children in teaching them to use their hands and their imagination. Here money is well spent in getting the best instructors available who can stimulate creative ability and latent initiative among the campers as well as teach them new and useful things to make.

PLAY AREA

Play space is important. The ideal acreage for a camp as set up by minimum standards of the American Camping Association is an acre per child or more. This allows for hiking, outdoor sports and activities of all types. We have provided a baseball diamond, archery court, tennis court, outdoor theatre, many camping sites and other special sites within the camping boundary.

Swimming Pool. If there is any single item of great importance during the camp season, it is swimming. It is a fine type of exercise and is refreshing. If such a camp is located on a lake or a good-sized stream, these can be utilized for this purpose. We were not so fortunate. Having no open body of water, we had to build a swimming pool. This required drilling a well for the additional water supply. To maintain the pool, all hygienic measures connected with swimming pools are carried out.

Outdoor Kitchen. Even though children are in a camp proper, they want their excursions, their hikes. Thus an outdoor kitchen at some distance from the main camp fulfills such a need. Here smaller children can have a picnic or overnight hike in order to learn primitive camping, self-reliance and improvization as they will have to take their own insulin, cook and weigh out their own food, etc., under supervision. Yet they are within easy reach of the camp. We built our outdoor kitchen on the edge of the property. It has a roof supported by four huge chestnut uprights. The stove is of stone with ample cooking surface and a dutch oven. Other facilities are storage sheds and a pony barn.

THE STAFF

Some mention has already been made of staff members. Their duties are briefly outlined: The medical director directs the general medical care of the campers, makes any changes in insulin dosage that are indicated by blood sugar studies. He meets any medical emergencies that may arise from time to time. There is a resident physician to assist the medical director.

The nurses carry out the instructions of the physician. They give all the insulin, etc., exactly as in any hospital. The night nurse has her special duties of general supervision of the entire camp and is especially on the lookout for reactions or impending acidosis. The nurses do not wear uniforms. They wear the same type of sensible camp clothing as the counsellors for medical care and supervision, which though ever present, is kept in the background.

The dietitian has full charge of the diets, the buying of food and the serving of the meals. The cooks work under her supervision.

The counsellors have their special duties according to their assignment. Young counsellors of mature judgment are preferable as they can enter into the spirit of the camp and be a part of it. They should be of high caliber and of special training so that they will have something to offer to the children and command their respect.

A maintenance man is general utility man for the entire camp and should be responsible to the director.

CAMP PROGRAM

The camp program has developed along the most modern and progressive trends in group activity. Because of the very highly specialized medical regimen which must be adhered to for the child's safety, there is a skeleton schedule of waking, eating and sleeping, around which the rest of the program revolves. Usually it develops as the days pass, according to the interests and inclination of the children, having no pre-camp pattern set for it. The counsellors who are highly trained, resourceful people, are capable of guiding or assisting the campers in their projects.

In this way the greatest amount of creativeness has been stimulated. The campers gain the highest degree of satisfaction from their experience because they have planned it themselves within their own groups, instead of following a predigested schedule cooked up before their arrival. Many graduate students have taken their group-work training at Ho Mita Koda.

FINANCES

To build such a camp involves a considerable investment. Just how much, will depend largely on the particular community and the cost of labor at the time. To start with it will represent an investment of at least $50,000.00. Then there is the equipment, the upkeep and the depreciation to consider. The present worth of our camp with the equipment is about $75,000.00. This does not include the upkeep, the depreciation and operational costs.

Let us consider the basic cost during operation as being $5.00 per child per day. This is low when we consider the double function of the camp, the camping proper plus the full medical care comparable to hospital care. Such a camp thus has two staffs and consequently double expense as compared with ordinary camps.

If we figure on one dollar per day per person for food, we get the following figures:

A. Food—50 children		
	$50.00 per day	
23 adults		
	$23.00 per day	
Total	$73.00 × 30 is	$2,190.00 per month
B. Staff Salaries—		$2,405.00 per month
Total		$4,595.00 per month

Income. The camp was incorporated on a non-profit basis to serve diabetic children according to their means. The top fee has been $100.00 per month. Very few children have been able to pay this sum. Most children have paid on a sliding scale from $100.00 to nothing. This means that supplementary sums have had to be raised to take care of operating and maintenance costs. In the past the Cleveland Foundation, the F. P. Fenn Fund and the Rose Fund and private gifts have helped to provide the needed money.

It is an expensive proposition but worth the investment in the pleasure it provides and the concrete results it obtains.

Reviews

Differential Diagnosis in Obscure Fever*

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ABNORMALLY high body temperature has been the subject of study by the clinician from as far back as ancient times up to the present day. A brief résumé of the development of knowledge of the mechanism of the production of fever, a classification of those conditions commonly associated with fever and a plan of diagnostic attack will be presented.

That Hippocrates was aware of fever and its importance as a prognostic sign there can be no doubt. Fever was regarded as an expression by the body of a disturbance of its humors. Recovery resulted from the elimination of the "concocted" humors (crisis) or diminution of secretion or increase in excretion (lysis).

No outstanding contribution to the subject of fever was made after Hippocrates' time until the invention of the thermometer by Galileo between 1593 and 1597.[7] Sanctorius, the father of the science of metabolism, began estimating the temperature of the human body with a thermometer in 1625. Although a clinical thermometer 3 inches (7.6 cm.) long was constructed by duVal in 1638, it was not accepted for general use. Between 1625 and 1745 Swammerdam, Haller and Martine kept the subject of thermometry alive from the viewpoint of physiology, but little or no clinical use was made of the instrument. De Haen in 1761 used thermometers in his clinic in Vienna.

In 1814, Davy clearly demonstrated the diurnal variation in body temperature. To Becquerel and Breschat (1835) is ascribed the determination of 98.6°F. (37°C.) as the normal mean body temperature.[9] In 1850, Traube challenged the Hippocratic "doctrine of the crises" and two years later published the first temperature curve to appear in the literature. He persuaded Wunderlich,[17] an associate at Leipsig, to study clinical thermometry. In the next fifteen years he studied about 25,000 patients. In 1868 he published his classic monograph and established the fact that the course of certain diseases is revealed by the course of the body temperature.

Until 1867 when Allbutt invented a self-registering mercury thermometer, the thermometers in use were ungainly and inaccurate. Wunderlich's instrument was a foot long and had to be held in the axilla for twenty minutes. Small wonder that thermometry for clinical investigation was unpopular!

With the advent of a fairly accurate method of estimating body temperature, the study of metabolism begun by Sanctorius became a major undertaking. Outstanding among the men in this field has been DuBois[9] who first became interested in the subject when he was a hospital orderly in the Spanish-American war carrying water to typhoid fever patients. In his monograph he has shown by calorimetric studies on normal human beings that production of heat by the body always equals the loss of heat.

On the basis of many studies in which human beings, normal and diseased, were subjects, DuBois concluded that the rise in

* From the Mayo Foundation, Rochester, Minn.

temperature in fever does not depend on the level of production of heat or change in production but is due to an adjustment which keeps elimination of heat below production. This adjustment is made by the temperature regulating mechanism. Liebermeister[13] has likened this to setting the regulating mechanisms at a higher level.

The thermoregulatory centers have been fairly well localized by Ranson.[14] Centers controlling loss of heat are in the preoptic and supraoptic regions between the anterior commissure and optic chiasm. The center controlling production and conservation of heat is located in the caudal part of the lateral hypothalamus. It appears to be identical with the sympathetic centers. Best and Taylor[4] stated: "From observations of patients with intracranial lesions involving the base of the brain, it seems most likely that in man the centers are situated as described by Ranson and his associates for animals. Lesions in the supraoptic region are associated, not uncommonly with hyperthermia; hypothermia, on the other hand, may accompany lesions involving the posterior part of the hypothalamus."

The thermoregulatory centers are influenced in three ways: (1) reflexly from the skin, (2) by the temperature of the blood flowing through them and (3) by toxic substances in the blood.

Hewlett[12] stated that, "in true fever, heat regulation is present but perverted." Hence lesions of the brain involving the thermoregulatory centers are not the cause of true fevers. Actually this question is of more than academic interest in differential diagnosis since, when a patient has a constant high temperature which will not respond to the usual measures for lowering of fever, the postulation that a lesion of the brain is present is warranted.

Before consideration of the diagnosis of the cause of fever, it may be well to review the causes of elevated temperature which are physiologic, rather than pathologic. Temperature may rise to 104°F. for a short time after strenuous exertion. A convulsion in which hysteria is the etiologic factor may cause a rise in the temperature by the same mechanism. Digestion may cause a rise of from 0.5° to 1.0°F. A low grade fever is not unusual in the first trimester of pregnancy. The temperature gradually falls to normal after this period. A rise of several degrees may result from dehydration of body tissues. Patients of whom the physician must be wary are malingerers who may raise the thermometer reading by physical means.

CONDITIONS IN WHICH FEVER OCCURS

The following classification of the pathologic causes of fever is a useful tool in differential diagnosis and includes most of the possible causes. The classification includes: (1) Congenital conditions and birth injuries, (2) trauma, (3) mechanical factors, (4) toxic agents, (5) infectious diseases, (6) neoplastic diseases and (7) miscellaneous conditions.

Congenital Conditions and Birth Injuries. Concerning these little need be said since they are relatively unimportant causes of fever. Among them may be mentioned injury to the brain at birth, but according to Hewlett this would not be a true fever if control of temperature were lost. Reports appear in the literature from time to time of cases of so-called habitual hyperthermia.[15] The patients have a temperature of 99° to 101°F. (37.2° to 38.3°C.). Another condition which might be included in the congenital group is the fever associated with so-called constitutional psychopathic inferiority.[1]

Trauma. Thermal reactions which occur after cystoscopy, gastroscopy or bronchoscopy, so-called fracture fevers, and the slight rise in temperature following operations when no infection is found to account for the fever may be considered to be a result of trauma. Fever may be attributed to trauma in these cases when marked

leukocytosis is absent and the fever is short lived. However, secondary infection may supervene.

Fever which occurs after crushing injuries usually begins as simple fracture fever augmented by a toxic factor from the products ot tissue destruction and maintained if the toxic element is severe or secondary infection sets in.

Mechanical Factors. Fever may result from factors which act directly on the centers that control temperature. For instance, following spinal tap the lowered pressure of the cerebrospinal fluid disturbs the thermoregulatory center. Other factors may act directly on the mechanism of dissipation of heat and fever will occur. In ichthyosis heat cannot be lost from the skin by the mechanism of vaporization, although some heat may be lost by radiation by the skin.[3]

Toxic Agents. Fever may occur in reactions to common drugs, such as alcohol, arsphenamine, iodides, bromides, belladonna, morphine and occasionally barbiturates. The diagnosis in many drug fevers is suggested by concomitant skin rash. By far the most important drug fever today is that due to sulfonamides. In a recent six months' period in a busy city hospital no less than one fever of obscure origin resolved each month when administration of sulfonamide compounds was discontinued.

Among other toxic reactions which cause fever may be mentioned all foreign protein reactions (including transfusion reaction) and reactions to pyrogens in rubber tubing.

In a broad sense fever associated with hyperthyroidism, heart failure and heat stroke fits into this group. Death of tissue in any part of the body may liberate toxic substances which cause fever. This occurs in pulmonary or myocardial infarction.

Infectious Diseases. In the diagnosis of infectious disease, not only the usual bacterial and parasitic infections of peacetime but also the tropical diseases which were introduced in this country during and since the war must be differentiated. Since most bacterial disease can be diagnosed readily by isolation of the offending organism and most contagious diseases by the clinical picture, this relatively large group of fever producing diseases will not be considered in detail. Diagnosis of some infectious diseases will be considered in a later section.

In the absence of any positive history or physical findings the presence of fever should suggest the possibility of hidden infection. Perinephritic abscess may not cause marked pain and may elude diagnosis until a complication, such as rupture into the kidney, occurs. Usually, however, some tenderness and spasm of the loin is present and leukocytes number from 20,000 to 30,000 per c. mm. of blood. The abscess is usually metastatic and the primary lesion, such as a small furuncle on the skin, may be insignificant.

Another difficult diagnosis is hepatic abscess. It may occur many years after an amebic infection of the colon or it may occur only a few days after a pyogenic infection such as acute cholecystitis or acute appendicitis. Confirmatory findings in the pyogenic type are pain in the region, enlargement of the liver and septic type of fever.

Although histoplasmosis is a rare disease, it would be diagnosed more frequently if it were considered as a possibility in all diseases characterized by chronicity, fever, emaciation, leukopenia and splenomegaly.

Neoplastic Diseases. Just what mechanism produces fever associated with neoplasm is open to conjecture. Undoubtedly, toxic-degenerative processes play a part but frequently no evidence of necrosis is seen in microscopic sections of the tumor. From the diagnostic point of view, the mechanism is not so important as the fact that the fever does occur. Neoplasm should be considered in all cases of fever of unknown cause but

particularly in cases in which adequate diagnostic procedures and therapeutic trials have not revealed infection. Fever may be the sole symptom for many weeks in the early part of the illness of a patient who has bronchogenic carcinoma.

In a study of 238 cases of carcinoma in various sites Briggs[5] found that in more than a third fever was noted in some phase of the illness. He stated, however, that its occurrence as a pronounced feature of the disease is an unusual finding. He found that fever was present in 60 per cent of cases of carcinoma involving the lung and pleura. Another point to bear in mind is that a lung abscess occasionally may result from the breakdown of a neoplastic process.

Miscellaneous Conditions. At least 95 per cent of the cases in which the temperature is abnormally elevated can be classified in the foregoing six main groups. In the seventh (5 per cent of cases) fall the miscellaneous conditions in which the cause of fever is obscure. In some of these conditions the cause of fever may be toxicity, infection or neoplastic diseases associated with destruction of tissue.

Among the more important of the miscellaneous conditions are: periarteritis nodosa (fever in 80 per cent of cases),[11] verrucous non-bacterial endocarditis, disseminated lupus erythematosus, blood dyscrasias such as leukemia, diabetic acidosis, bleeding duodenal ulcer (fever in 80 per cent of cases), cirrhosis of the liver (in 50 per cent of cases),[10] psychogenic fever and fever of unknown etiology.

Dill and Isenhour[8] in their study of the cause of fever in cases of bleeding peptic ulcer made control studies of normal subjects. When they introduced blood into the gastrointestinal tract no fever occurred.

DIAGNOSIS

The diagnosis of an unexplained fever is one of the most difficult problems in medicine and for this very reason one of the most interesting and satisfying to the clinician when a correct diagnosis is attained. Truly, the study of fever is the study of medicine because the cause of fever may be related to any organ or any tissue in the body.

History. As in all diseases, this is probably the most important when a clear-cut story can be obtained. Geographic location, contact with either human beings or animals that may have an infectious disease, and periodicity of fever should always be considered.

Because the geographic locations of endemic areas of disease should always be kept in mind in eliciting a history the clinician will do well, in these times, to provide himself with maps showing the endemic areas of such diseases as malaria, typhus and histoplasmosis. It is also important to ask the patient about his contact with persons who have contagious disease. Contagious diseases, particularly those in which skin rash is not present, should be considered in the differential diagnosis.

Frequently the type of temperature curve shown by observation of the patient for several days or weeks will give a hint as to the diagnosis in malaria, Hodgkin's disease (Pel-Ebstein fever) and the response of rheumatic fever to salicylates. The monograph by Ask-Upmark on periodic fever is well worth reading.[2]

If a veteran who has returned recently from New Guinea complains of chills and fever which occur every other day, malaria certainly would be considered as the first possibility. Brucellosis would be the first consideration when the patient is a farmer or even a city dweller whose fever began shortly after he drank unpasteurized milk. If a patient relates that he has dressed wild rabbits, the possibility of tularemia must be considered.

Probably the most important factor in establishing toxicity as a cause of fever is the history. Frequently when a patient is asked if he has taken any medicine or drugs lately the answer will be "No" but on further questioning he may say that he has been taking a tonic which frequently proves to be "Doctor So and So's nerve elixir," which contains bromides. When a patient who is not being given any medication has a fever in the immediate postoperative period, the internist will do well to bear in mind the routine at operation of placing 5 Gm. of one of the sulfonamide drugs in the peritoneal cavity or surgical wound. Fever has resulted from reaction to just this relatively small amount of the drug.

In interpreting the history the negative side must also be given consideration. Drug fever may occur although the patient has not ingested the drug by mouth. A negative history of alcoholism does not rule out cirrhosis of the liver.

Certain patients may interfere with the taking of a good history involuntarily by stressing the importance of fever when actually it causes no distress.

Physical Examination. Special attention should be given to the search for rashes, incipient jaundice, enlarged lymph nodes, nodules on vessels or in muscles, hard prostate gland, tender regions in bone, small draining sinus and pathologic fractures. In rare instances, barbiturates will cause a rash and fever almost indistinguishable from scarlet fever. In these cases it is well to isolate the patient even though the diagnosis of drug fever is the more likely one.

Laboratory Studies. Serologic studies, repeated cultures, determination of the sedimentation rate, and smear and culture of the blood often will yield important diagnostic information. In a case in which the presence of histoplasmosis is suspected, smears of the peripheral blood will at times show parasitized mononuclear cells. Sternal puncture will reveal a greater number of positive smears. Cultures which are thought to contain Histoplasma capsulatum should be kept a month before being declared negative.

Urinalysis and culture of the urine should be carried out. If, for any reason, the presence of ova or parasites in the gastrointestinal tract is suspected, the feces should be examined. Erythrocyte, leukocyte and differential counts should be made. It should be borne in mind that absence of eosinophilia rules out neither periarteritis nodosa nor trichinosis. Blood agglutination tests for typhoid, paratyphoid, tularemia and brucellosis should be made when the presence of one of these diseases is suspected. The diagnosis of rickettsial diseases can be made or ruled out when the Weil-Felix complement fixation is carried out. All the rickettsial diseases are important and a positive Weil-Felix reaction should be looked for. To differentiate Rocky Mountain spotted fever from other rickettsial diseases a complement fixation test should be performed. Results become positive during the second week of the disease.

Examination of gastric washings and sputum are particularly useful in the diagnosis of tuberculosis. Neoplasms of bone and lesions due to metastasis from prostatic carcinoma may be diagnosed from the results of determination of the acid and alkaline phosphatase in the blood. Determination of the basal metabolic rate may be a useful procedure. In fevers associated with hyperthyroidism and infection the basal metabolic rate is increased. It is normal in habitual hyperthermia. It may be normal in hyperthermia due to a brain lesion.[15]

Several pitfalls common to the interpretation of the results of all diagnostic procedures must be borne in mind. A positive result of the agglutination or skin test for Brucella is not necessarily diagnostic of brucellosis. Also if the sedimentation rate

is high and results of the agglutination test are positive some condition other than brucellosis is probably present for in brucellosis the sedimentation rate is relatively low to normal.[6] Diagnosis of brucellosis is best made by positive blood culture, for the fact that the patient has been in contact with infected animals does not necessarily mean that he has become infected.

In the absence of positive findings on examination of the sputum or gastric washings and on subsequent inoculation of guinea pigs the diagnosis of pulmonary tuberculosis is best made by means of serial roentgenograms. Negative results of examination of gastric washings on several successive days merely mean that the patient is probably not a menace to his family. They do not rule out the diagnosis of tuberculosis.

Roentgenologic Examination. Roentgenograms of the pelvis, thorax and long bones may reveal evidence of the pathologic condition which is causing the fever. Evidence of metastasis may be found in long bones and presence of stones in the pancreatic region may be noted. Roentgenologic examination of the gastrointestinal tract may be necessary to rule out the presence of a polypoid type of neoplasm which is asymptomatic until it has metastasized.

Laparotomy. Walters and Snell[16] have reported a case of cholecystic disease in which intermittent fever was the only symptom. There was no jaundice, no pain and no roentgenologic evidence of stones. Yet, on laparotomy stones were found in both the cystic and the common ducts. Mention is made of this to show that sometimes laparotomy serves as a diagnostic procedure in unexplained fever. Whether it is warranted or not is a moot question.

Therapeutic Tests. Several therapeutic tests are helpful in establishing the type of fever. Fevers due to infections can be treated successfully by administration of antipyretics but the temperature rarely falls when narcotics are given. The elevated temperature in habitual hyperthermia and the "neurosis" type of fever is not reduced by administration of antipyretics but is reduced when morphine or some other narcotic is given.

Antibiotic and chemotherapeutic agents can eliminate fever due to infection by terminating the infection. Administration of these agents is a standard procedure in the diagnosis of unexplained fever after drug fever has been ruled out. These drugs rarely reduce the fever unless some infection has been overlooked in the other diagnostic procedures.

Another confusing point in the toxic picture when a reaction due to the sulfonamide drugs occurs in older people is the association of cerebral symptoms which sometimes leads to a mistaken diagnosis of cerebral vascular accident. The quick recovery of these patients when they drink a glass of water every hour and are given a little sodium bicarbonate rules out the possibility of cerebral infarction. Also the blood pressure tends to stay at a fixed level in toxic reactions. A therapeutic trial of emetine may confirm the presumptive diagnosis of amebic abscess of the liver even when results of examination of the stools are negative.

Treatment with roentgen rays may be given when a presumptive diagnosis of lymphoblastoma has been made. This sometimes gives surprisingly gratifying results.

Microscopic Examination. Biopsy of a node, vessel or nodule in skin or muscle may be the only positive means of diagnosing lymphoblastoma, periarteritis nodosa or trichinosis. In a small number of cases a diagnosis cannot be made even at necropsy.

SUMMARY

True fever is due to a disturbance of the thermoregulatory centers. Fever results

when these centers keep elimination of heat below the level of production.

The usual causes of fever can be grouped under the following headings: congenital conditions and birth injuries, trauma, mechanical factors, toxic agents, infectious diseases and neoplastic diseases. This group accounts for about 95 per cent of all fevers. A few conditions which do not fit under these headings but which always should be considered in the differential diagnosis are: periarteritis nodosa, verrucous endocarditis, disseminated lupus erythematosus, blood dyscrasias, diabetic acidosis and cirrhosis of the liver.

A plan of diagnostic attack has been presented, the main features of which are: (1) critical evaluation of the history, (2) critical evaluation of the laboratory findings and (3) emphasis on alertness for evidence of malignant disease.

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Treatment of Severe Functional Headaches

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THE pathogenesis of headaches has been the subject of extensive and fruitful investigation during the past decade. A number of etiological factors have been uncovered and many of the older beliefs have been subjected to critical appraisal. For instance, the experimental studies of Eckardt et al.[4] have shown that myopia (artificially produced) will not cause headache, contrary to common belief. However, astigmatism and hypermetropia will do so. Williams[12] recently classified sinus headaches as an allergic phenomenon involving the cranial muscles. Horton et al.[8] have described a peculiar syndrome of headache associated with sweating, lachrymation and other phenomena which can be precipitated or reproduced by injections of histamine; in these cases the vasodilator action of histamine is said to be the causative factor. In a recent discussion of the pathogenesis of headaches Wolfe[13] outlined the chief mechanisms as follows: (1) spasm of the cranial or cervical muscles; (2) compression, traction or inflammation of the sensory cranial or cervical nerves; (3) traction on or displacement of the large veins and adjacent dura. (4) distention, traction and dilatation of the intracranial and/or extracranial arteries. In keeping with this last mechanism are the findings of Atkinson[2] who believes that the scotomas of migraine are vasoconstrictor phenomena while the headache itself is a secondary vasodilator reaction.

The manifest importance of vasomotor disturbances as a factor in the pathogenesis of functional headaches has led to the investigation of drugs which alter the cerebral circulation. The nicotinic acid group has been studied intensively both experimentally and clinically.

The free nicotinate radical is directly responsible for the vasodilator activity of sodium nicotinate, nicotinic acid, the other ionizable salts and even quinine nicotinate. The amide (nicotinamide) and the diethylamide (coramine) have no vasodilator activity.[3] The vascular action of the nicotinate radical is opposed by adrenalin[3] and is not synergized by prostigmin,[9] showing that its action is directly on the blood vessels and not via the autonomic nervous system.

Moore[10] studied the effect of niacin on the pial vessels by direct visualization and was able to photograph the vasodilatation it produced. Aring et al.[1] measured the cerebral blood flow and found that increased circulation persisted for as long as an hour after intravenous injection of 100 mg. of niacin.

Limited reports of the clinical value of these vasodilators have appeared in the literature from time to time. Rogers[11] mentioned one case of migraine in which the attacks could be aborted by 100 mg. of nicotinic acid in oral doses; Enrique[5] described the dramatic relief of a single acute attack of migraine by 100 mg. intravenous dose of nicotinic acid. Atkinson[2] has reported good results in the prolonged treatment of "histamine-negative" migraines with oral and parenteral niacin. Williams[12] administered courses of oral and intra-

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muscular niacin for sinus headaches with relief in 69 per cent of seventy-eight patients. Zeligs[14] recently reported twenty-five cases of malarial headaches, resistant to all the usual drugs such as ergotamine tartrate, analgesics, etc. One hundred mg. doses of niacin provided complete relief in 40 per cent, moderate relief[6] in 32 per cent.

In a recent paper, one of us (J. W. G.) reported the results of treatment of 100 consecutive cases of severe headache, regardless of etiology, with sodium nicotinate intravenously. Seventy-five per cent were completely relieved by a single injection and 9 per cent had only minimal recurrence within 24 hours. Since the publication of these data we have treated a considerable number of patients with migraine, and severe idiopathic headache, and a few more patients with cephalalgia following lumbar puncture. The results have continued to be as favorable as previously reported. This later material, however, could not be followed as closely nor investigated as carefully as the hundred original cases and hence does not lend itself for statistical comparison.

There is another factor in the pathogenesis of migraine and related headaches which is of the greatest importance. It has been shown[7] that there often is an easily demonstrable disturbance of tissue hydration (i.e., salt and water metabolism) in patients suffering from such headaches. It is a generally recognized fact that migraine occurs more commonly during the premenstrual period and during menopause, when disturbances of salt and water metabolism are nearly always present. In a series of 150 cases of migraine and migraine-like headaches which were submitted to electrolyte balance studies, it was found that 90 per cent of the patients showed definite water retention and 84 per cent showed retention of sodium chloride under the conditions of a salt tolerance study. Correction of the metabolic disturbance resulted in complete cures in 44 per cent, great improvement (reduction of headaches to mild, occasional attacks) in an additional 25 per cent, improvement in 21 per cent and failure in 10 per cent.

THERAPEUTIC APPLICATIONS

Appreciation of the importance of these two factors (i.e., vasomotor disturbances and changes in tissue hydration) has led to many innovations in the methods of headache therapy and to increased efficacy of treatment.

Intravenous sodium nicotinate may prove to be a valuable therapeutic tool if used with discretion. Indications for its use are as follows:

1. It must always be kept in mind that such vasodilator therapy is purely symptomatic, and as far as we know, will not alter the severity or frequency of subsequent headaches in patients suffering from migraine or other recurrent forms of functional cephalalgia.

2. Intravenous sodium nicotinate should be used only for severe headaches. A patient with a mild headache will not be thankful for the manifest discomfort of the flush and thermesthesia which an intravenous dose of 100 mg. will produce.

3. It appears that such vasodilator therapy is particularly effective in the immediate treatment of migraine and migraine-like headaches, as well as of those following lumbar puncture, air encephalography or similar procedures. At the present time we believe that sodium nicotinate is to be preferred to the usual drugs employed in these conditions. There is no other way short of the use of powerful narcotics to alleviate the headaches following a lumbar puncture. The use of ergot derivatives such as ergotamine tartrate and ergonovine is subject to certain disadvantages. A relatively large proportion of patients do not tolerate these

drugs well; the gastric symptoms may be most distressing. The danger of ergot poisoning, though remote, must always be kept in mind when dealing with patients who suffer chronically with migraine. By way of contrast, sodium nicotinate is a non-toxic drug: 1,000 mg. per kilo body weight may be given to dogs for prolonged periods without any ill effects. In man, slight nausea may be felt during the flush; very rarely actual vomiting occurs. We have seen only a single instance of this reaction.

Contraindications to the use of sodium nicotinate are few. As already pointed out, it is too potent an agent to be used in mild headaches. The other feature which must be considered is that of dosage. The 100 mg. intravenous dose which we have used was selected arbitrarily as being large enough to produce vasodilatation in almost every instance. It may be wise, as with every other drug, to suit the dose to the patient, those with evidence of vasomotor instability (such as blushing on slight psychic stimulus, etc.) requiring smaller doses.

We have not found oral therapy to be of value.

The second aspect of the therapeutic approach aims at correcting the underlying salt and water imbalance if present. Clearly, such therapy is not merely symptomatic but is directed at an underlying etiological factor. Correction of this factor may bring about permanent alleviation of the recurrent headaches. The presence of salt and water retention may be demonstrated quite simply by the salt tolerance test. This is carried out as follows:

The patient is instructed to eat and drink exactly the same things, in identical quantity, for two consecutive days. Separate twenty-four-hour urine specimens are collected on these days. At 10 A.M. of the second (test) day the patient is given 10 Gm. of enteric-coated salt tablets and 250 cc. of water to drink. Total urinary chloride excretion on both days is determined by the usual laboratory method. If the patient does not excrete at least 7 Gm. more salt on the second day, and if he does not put out 200 cc. more urine on the second than on the first day, definite salt and water retention is present.

Salt and water retention can be demonstrated, appropriate therapy will give excellent results in at least 70 per cent of cases. Therapy is aimed at reduction of tissue salt and water as well as at decrease in vasomotor instability. The means by which this may be done are as follows:

1. High-protein, low-carbohydrate diet. High protein diets are definitely diuretic, partly because of their purine content and partly because of the resulting stimulation of certain endocrine glands. Carbohydrates, on the other hand, are antidiuretic, possibly by stimulating increased insulin production. Underweight patients should receive adequate supplements of fat to prevent any undesirable loss of weight.

2. Limitation of fluids to 1,500 cc. per day.

3. Reduction of dietary salt intake to an absolute minimum.

4. Diuresis for simultaneous removal of water and tissue salt. This is accomplished by alternate weekly courses of ammonium chloride 0.5 Gm., three times a day, and potassium acetate or gluconate 0.5 Gm., three times daily. In severe cases, injection of small doses of posterior pituitary extract may be valuable, for the transient antidiuretic effect of this hormone is followed shortly by an increased excretion of sodium chloride.

5. A combination of atropine (0.2 to 0.3 mg.) with phenobarbital (15 mg.) three times a day should be used to combat vasomotor instability.

A therapeutic response to this regimen, as evidenced by a diminution in the frequency and severity of the headaches, should be-

come apparent within about two weeks. During this time attacks may be treated with sodium nicotinate as outlined above. The dehydration routine should be maintained rigidly for at least two months, after which treatment may gradually be reduced and eventually withdrawn. However, the basic features of this antiretentional regimen, namely, fluid and salt restriction as well as high-protein, low-carbohydrate diet, should be continued by the patient. Attention to these dietary limitations should not prove overburdensome to the patient, especially when it means freedom from incapacitating headaches.

There is a type of migraine patient who develops attacks premenstrually, yet contrary to the findings in the majority of these cases, performance of the salt tolerance test shows no retention of salt. As a matter of fact, the sodium chloride excretion of these patients on an unlimited diet is usually quite high, well above 10 Gm. per twenty-four hours. These patients, who are underweight as a rule, do not respond to the treatment outlined above, quite in accord with the theory which does not lead us to expect beneficial results from further increased losses of sodium chloride. Hence we tried a different approach in a small group of such cases: Adrenal cortical extract was administered both orally and parenterally a few days before the expected attack. This treatment successfully prevented the onset of migraine headaches in all twelve patients in which it was tried.

The number of observations so far is much too small to draw conclusions, nor do the data available at present explain the mechanism by which the cortical hormone interferes with the development of a migrainous state. The well established antihistamine effects of the cortical hormone deserve consideration. One could also propose, as another explanation, that the cortical hormone accomplishes results by correcting disturbances of electrolyte metabolism. In the meantime, until further data become available to establish a sound basis for hormonal therapy, the use of this experimental approach seems justified in migraine cases of the premenstrual type in which salt retention is not demonstrable by the salt tolerance test.

The indications for each of these methods of therapy are quite clear. Vasodilator therapy is indicated for the isolated episode of severe cephalalgia, especially following lumbar puncture or similar procedures. It is also used to alleviate migrainous attacks while the slower acting therapy of antiretentional regime is brought into play. The intelligent combination of these two procedures should provide both symptomatic relief and permanent therapeutic effect in most cases of migraine.

CONCLUSIONS

1. The mechanisms involved in the production of headaches are reviewed briefly and the importance of vasomotor changes and disturbances in tissue hydration are discussed.

2. Methods of therapy based on the correction of these two factors are outlined on the basis of two series of 100 and 150 patients, respectively.

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Seminar on Antibiotics

Penicillin in the Treatment of Syphilis*

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SYPHILIS is a disease of such exquisite and capricious chronicity that an evaluation of the ultimate results of any form of therapy requires a prolonged period of post-treatment observation. Penicillin has been used in the treatment of syphilis for but a few years. Hence, discussions of its use in this disease necessarily must be tempered, being subject to revision perhaps even in the immediate future.

Factual data on penicillin in syphilotherapy have accumulated with meteoric rapidity. This has been possible only because it has been studied on a cooperative and integrated nationwide basis. In September 1943, only three months after Mahoney's original report[1] that *T. pallidum* is susceptible to the action of penicillin, a cooperative study of the effect of penicillin in the treatment of syphilis was organized under the auspices of the Committee on Medical Research. Participating in this study are forty-one clinics and eight laboratories of experimental syphilis. As a result of their collective efforts, an enormous amount of information has been compiled. In the first three years approximately 35,000 patients were treated, and the results (for early syphilis) reported to a central statistical unit. With these significant data available, preliminary evaluations of the early results of penicillin therapy are possible.

Even the most skeptical observer no longer denies that penicillin is a valuable adjunct to syphilotherapy, nor that it is, in some respects, superior to any previous form of treatment. That it has serious limitations is recognized by its most ardent protagonists.

The *ideal treatment* of syphilis would be that which is: (1) completely and uniformly effective, (2) entirely devoid of toxicity, and (3) readily administered with a minimum of inconvenience to the patient and to his physician.

Penicillin is effective, but not uniformly nor always completely so. It is, in marked contrast to metal chemotherapy, non-toxic, approaching the ideal in this respect. It is relatively easy to administer, and therapeutically effective amounts can be given in a comparatively brief period of time.

The principal *advantages* of penicillin in the treatment of syphilis are: (1) its lack of toxicity, and (2) the fact that the therapeutic schedule need not be inordinately prolonged. Consequently, the full course of treatment is almost invariably completed. This is not the case with any form of arsenotherapy in which toxic reactions increase in frequency the more the time interval is compressed, and in which case-holding becomes increasingly difficult as the duration of therapy is prolonged.

Penicillin is a relatively innocuous substance. The untoward reactions thus far reported to have followed its use have been confined almost exclusively to allergic manifestations in the skin.[2] These reactions

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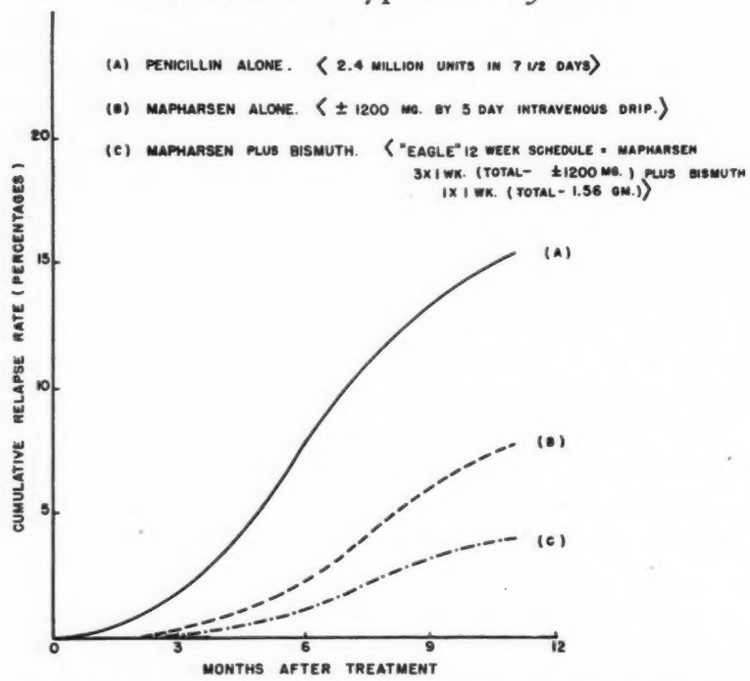


FIG. 1. Cumulative percentage relapse rates with treatment schedules utilizing; (A) penicillin alone (2.4 million units); (B) mapharsen alone (1,200 mg.); and (C) mapharsen (1,200 mg.) plus bismuth (1.56 Gm.). USPHS data, smoothed curves.

may occur shortly after the institution of therapy as a result of a pre-existing hypersensitivity, or late in the course of treatment because of developing dermal sensitization. Delayed "serum-sickness-like" reactions occur, but are extremely rare.[3] The incidence of serious toxic reactions is negligible, for in less than one patient in several thousand[4] treated for early syphilis with penicillin do untoward reactions necessitate interruption of the course of therapy. Herxheimer reactions are frequent, especially in early syphilis, in which approximately 75 per cent of patients treated develop fever with transitory intensification of the early tissue reaction. Milian's syndrome ("Erythema of the Ninth Day") has not been reported.

The principal *disadvantages* of penicillin therapy (at least with any schedule of administration the results of which are presently available) are: (1) the probable essentiality of hospitalization, when the drug is given in aqueous solution, and (2) the significant number of treatment failures (relapse and seroresistance in early syphilis, sub-maximal improvement in certain forms of late syphilis).

The necessity for hospitalization of patients receiving penicillin as therapy for syphilis significantly reduces its general utility, for the number of hospital beds available for this purpose is limited. The United States Public Health Service has done much to obviate this difficulty through its in-patient Rapid Treatment Center program. Nevertheless, there are many to whom the necessary hospital facilities are denied.

To be feasible for ambulatory syphilis patients in the clinic and in the physician's office, a modified penicillin with prolonged activity is required. Many attempts have been made to extend the duration of penicillin action, either by delaying its absorption or by blocking its renal excretion. By far the most satisfactory modification presently available is the suspension of penicillin in peanut oil and beeswax devised by

Romansky and Rittman.[5] With a preparation containing 300,000 units of calcium penicillin with 4.8 per cent beeswax contained in 1 cc. of peanut oil, detectable blood levels can be maintained for approximately twenty-four hours following a single injection in 75 per cent of the patients treated.[6]

Penicillin in oil and beeswax ("POB") has been used in the treatment of syphilis. Preliminary reports[7,8] suggest that the results may be sufficiently satisfactory to warrant more widespread application. Treatment schedules utilizing POB alone and in combination with mapharsen or bismuth currently are being evaluated by the clinics cooperating in the nationwide syphilis study.

With any schedule of penicillin administration thus far studied, the incidence of infectious relapse and of seroresistance (in early syphilis) has been significantly higher than those with "adequate" metal chemotherapy. For example, the incidence of infectious relapse following 2.4 million units of penicillin in seven and one-half days has been approximately *five times* that with a twelve weeks' semi-intensive course of mapharsen and bismuth. (Fig. 1.)

Comparative ineffectiveness of penicillin is less than appears from this figure. Present information indicates 2.4 million units is a small total dosage and seven and one half days a brief period for administration. The data are for commercial penicillin; the therapeutic value of some is now known[9] to have been low because of its high content of penicillin K. This fraction, although active *in vitro* against the test strain of *Staphylococcus* used to determine its potency in terms of Oxford units, is destroyed in the body to a significant degree,[10] and is known to be decidedly inferior to other penicillin fractions in the treatment of experimental rabbit syphilis.[11] Also, the comparison of relapse rates following penicillin treatment with those of metal chemotherapy must be made with the knowledge that the recorded percentage of relapse refers only to those who actually completed the full schedule of therapy. Not indicated in Figure 1 is the fact that a sizeable proportion of patients who undertake ambulatory arsenobismuth therapy become delinquent, and fail to receive the full course of treatment.

A more satisfactory comparison between penicillin and metal chemotherapy in the treatment of (early) syphilis may be made by taking into account the three attributes of the "ideal" therapeutic agent: effectiveness, lack of toxicity and convenience of administration. (Table 1.)

TABLE 1

A COMPARISON OF PENICILLIN WITH METAL CHEMOTHERAPY IN EARLY SYPHILIS, IN RESPECT TO EFFECTIVENESS, TOXICITY AND CONVENIENCE TO THE PATIENT

	"Effectiveness" (as relapse rates after 11 months) Per Cent	"Toxicity" (as deaths due to treatment)	"Convenience" (as per cent of patients completing full course of therapy) Per Cent
Penicillin 2,400,000 units in 7½ days (40,000 units × 60).	15.3	0	99.9
Intensive Arsenotherapy Mapharsen 1200 mg. in 5 days by intravenous drip.	8.5	1 in 200[12]	96.5[13]
Semi-intensive Arsenobismuth Therapy Mapharsen 3 × 1 week (total 1200 mg.) Bismuth 1 × 1 week (total 1.56 Gm.) — 12 wk.	3.5	1 in 2000[12]	37.5[14]

Penicillin Resistance. Dunham, Hamre and Rake[15] have suggested, on the basis of animal experiments, that penicillin-resistant

strains may be developed by inadequate initial dosage. Tsun and Frazier,[16] however, report that spirochetes (Reiter strain), exposed *in vitro* to gradually increasing concentrations of penicillin, do not become less susceptible to its antibiotic action.

Thus far at least, penicillin-resistant strains of *T. pallidum* have been no serious clinical program. The only report of early lesions failing to heal under penicillin therapy is that of Tyson,[17] whose patient received 2.4 million units for seropositive primary syphilis over a period of *four days*, hardly a long enough time upon which to adjudge failure of response.*

On the other hand, lesions resistant to arsenobismuth therapy may heal satisfactorily with penicillin, as Nelson and Duncan[18] have demonstrated in their report of six such cases from this clinic.

PENICILLIN IN THE TREATMENT OF EARLY SYPHILIS

The major effort of the cooperative study thus far has been to define the usefulness of penicillin in the treatment of early acquired syphilis,[19] and in this condition information of some statistical significance is now available. There are, in early syphilis, several well defined end-points from which conclusions may be drawn: (1) the disappearance time of spirochetes from infectious lesions, (2) the healing of lesions, (3) the attainment of seronegativity and (4) the incidence of clinical and serologic relapse, most of which occur within the first year.

How good is penicillin in the treatment of early syphilis? There can be, of course, no simple and unqualified answer to this question, for there are several factors which influence the results of therapy. Among these are: (1) the duration of the disease, (2) the time-dose relationships, (3) the total penicillin dosage, and (4) the concurrent use of other antisyphilitic drugs.

Duration of Disease. As with all other forms of therapy, the earlier in the course of syphilitic infection penicillin is started the better will be the results. The common denominator appears to be the total number of invading organisms within the body of the host. In the cooperative study, the failure rate when the disease was of at least two months' duration was twice that among those treated within the first week of the disease. In the U. S. Army,[20] the failure rate in secondary syphilis was more than four times that of patients treated in the primary stage.

Time-Dose Relationships. There is ample evidence, both from the clinic[21] and from the laboratory[22] that the therapeutic effectiveness of penicillin is profoundly influenced by the method of its administration. In this respect, penicillin differs greatly from the arsenicals. The latter, being bound by the organisms of syphilis, are spirocheticidal in proportion to the amount of arsenic so bound,[23] which is in turn dependent upon the total quantity of arsenical to which the spirochetes are exposed. Thus, a higher arsenical concentration of short duration is as effective as a concentration half as great but maintained for twice as long.

Penicillin, on the contrary, is not bound by spirochetal organisms, and its activity depends upon *the length of time during which therapeutically effective levels are available* at the site of action. Precisely what the minimum effective level is and how long it must be maintained have not been determined. It is clear, however, that penicillin is actively spirocheticidal in extremely low concentrations. It also is evident that relatively low concentrations acting over a long period of time are far more effective than high concentrations of brief duration. Increasing the tissue levels of penicillin, by giving higher dosages per injection, tends to increase its

* We have recently observed a patient with a gumma of the penis that failed to heal with 4.8 million units of penicillin given over 15 days. The lesion healed promptly following therapy with mapharsen and bismuth.

therapeutic effectiveness in the treatment of syphilis, at least up to a certain point; but of far greater importance appears to be the time period over which *T. pallidum* is exposed to the action of the drug.

It has been presumed, largely from experiences with more acutely lethal infections, that in the treatment of syphilis it is desirable to keep the tissue levels of penicillin relatively constant throughout the course of treatment. Were this true, there would appear to be a theoretic advantage in administration by continuous infusion, either by intravenous or intramuscular drip. These methods, however, necessitate markedly restricted activity on the part of the patient, and may cause painful local reactions. In view of evidence[24] that blood levels following intermittent intramuscular injection are not markedly inferior to those of continuous infusion, and since satisfactory results have been obtained with the former method of administration, continuous parenteral administration seems neither necessary nor especially desirable.

Indeed, there is some evidence that constant maintenance of tissue levels may not be essential in the treatment of (experimental rabbit) syphilis. Eagle reports that in these animals, the interval between injections may be prolonged far beyond the usually recommended three-hour period without sacrificing therapeutic activity. He suggests that this is possible because *T. pallidum*, unlike many pathogenic bacteria, multiplies so slowly that a considerable period of time may elapse without a significant interim increase in the number of organisms. There is no clinical information to parallel this finding, although a favorable early response has been observed in small series of patients[25,26] treated on an ambulatory basis with aqueous solutions of penicillin, by schedules involving relatively long periods between injections during which no penicillin activity would be expected.

Total Penicillin Dosage. It is apparent from the above considerations that increased total dosages of penicillin will influence the results of therapy more if used to prolong the course of treatment than if given to augment the blood level at any one time.

With the time factor constant, the clinical results indicate a higher "cure" rate following 1,200,000 units than after 600,000 units. Results with 2,400,000 units are superior to those with 1,200,000, but the difference is less striking. With larger doses, there still are insufficient data, but with 4.8 million and 9.6 million units, it may be that the law of diminishing returns will become apparent.

Concurrent Use of Other Antisyphilitic Drugs. Eagle and his co-workers[27] have demonstrated that when penicillin and mapharsen are administered concurrently to syphilitic rabbits the therapeutic effects not only are additive but actually synergistic. A similar synergism between penicillin and bismuth also has been suggested.

This important laboratory observation has been studied by the clinics cooperating in the Penicillin Study, and the clinical results following the use of penicillin with mapharsen have been superior to those with penicillin alone.[19] Administered in combination with bismuth, the results also are better than with penicillin alone. So significant does the U. S. Public Health Service consider this development that at its various Rapid Treatment Centers, the concomitant administration of penicillin, mapharsen and bismuth now is used routinely.

Recommendations for the Use of Penicillin in Early Syphilis. It is possible, on the basis of the facts now available, to outline in general terms certain recommendations for the use of penicillin in the treatment of patients with early syphilis. These are personal, and, as will be seen, involve both larger total dosage and longer duration of treatment than in previously published papers.

It is most convenient to start with an arbitrarily selected total penicillin dosage, which for seronegative primary syphilis should be a minimum of 3.0 million units; for seropositive primary syphilis, at least 5.0 million units; and for secondary syphilis, no less than 7.0 million units. Preparations with a minimal content of penicillin K are essential. Repeated intramuscular injections are preferred to other technics of administration.

With Aqueous Penicillin:

1. Hospitalization and administration throughout the day and night is desirable, if only to shorten the duration of treatment for the sake of convenience and case-holding.

2. Individual injections probably should not exceed 50,000 units. Further increases in the dosage per injection probably entail a progressive waste of penicillin.

3. A satisfactory interval between injections is three hours. When the time factor is important to the patient, the interval may be compressed to two hours, although perhaps at the expense of a slightly higher failure rate.

4. The total duration of treatment under these conditions would be *at least:* (1) seronegative primary, 7½ days, (2) seropositive primary, 12½ days, and (3) secondary, 17½ days.

With Penicillin-Oil-Beeswax: *

1. May prove to be feasible for use in the out-patient clinic and in the physician's office.

2. Tissue concentrations can be maintained for reasonably long periods of time in most cases with single daily intramuscular injections of 300,000 to 600,000 units each.

3. Occasional brief (twenty-four-hour) lapses in treatment (e.g., on Sundays when hospital clinics are closed) theoretically should detract little from therapeutic effectiveness.

4. The total duration of treatment probably should be at least: (1) seronegative primary, 10 days, (2) seropositive primary, 17 days, and (3) secondary, 23 days.

Whether metal chemotherapy should routinely be given concomitantly with the course of penicillin is largely a matter of personal preference. There is ample evidence that the combination is more effective than is penicillin alone. It is recognized, however, that the administration of arsenicals introduces a risk of serious reactions in direct proportion to the total amount of the drug, and in inverse proportion to the time interval over which it is given.

In view of this and other considerations, opinion is divided as to the desirability of combining penicillin and mapharsen in the routine treatment of early syphilis. The opinion of a majority of a group of competent syphilologists[19] acting in an advisory capacity to the National Institute of Health is that the results of penicillin alone, when administered in adequate amounts over a long enough period of time, are satisfactory in a sufficiently large proportion of patients to justify eliminating arsenicals from the *original* course of treatment, reserving its use for relapsing cases. Schoch and Alexander[28] believe that a combination of penicillin and bismuth offers a satisfactory compromise, one which increases therapeutic effectiveness without significantly adding to the risks of therapy.

Whatever schedule of therapy is used in the treatment of early syphilis, it is essential that the outcome be determined by frequent post-treatment observations. Follow-up studies, including careful examinations for clinical evidences of relapse and serial *quantitative* serologic tests, should be made monthly during the

* It should be stressed that as yet there are available no significant data to support *any* arbitrary scheme for the use of POB in the treatment of syphilis. Unit for unit, POB may, in my opinion, be expected to prove inferior to comparable amounts of aqueous penicillin given in divided doses every two to three hours. Hence, not only should larger amounts of POB be used, but the total duration of therapy should be longer than with aqueous penicillin.

first year, and at gradually increasing intervals thereafter. The spinal fluid should be tested approximately six months following the completion of treatment.

Effect upon the Evolution of Syphilis of Small Doses of Penicillin. In penicillin a drug effective against both syphilis and gonorrhea is available for the first time. This fact raises the cogent question of the effect upon simultaneously acquired syphilitic infection of small doses of penicillin such as are used in the treatment of gonorrhea.

There is evidence that small doses of penicillin may either (1) prolong the incubation period and delay the serologic response, (2) modify or suppress completely the early tissue reaction, or (3) actually abort the disease.

Under these circumstances, patients with gonorrhea who also have suggestive signs of early syphilis should not receive (small doses of) penicillin until the possibility of a dual infection can be excluded. The presence of pre-primary syphilis should be seriously considered when patients receiving penicillin therapy for gonorrhea develop a constitutional reaction with fever, headache and malaise, which often is indicative of a Herxheimer reaction.[29,30]

All patients treated for gonorrhea with penicillin should be followed for at least four months, and periodically checked with examinations to detect clinical manifestations of early syphilis and with reliable serologic tests.

PENICILLIN IN NEUROSYPHILIS

A proper evaluation of the results of therapy in neurosyphilis requires: (1) an understanding of its spontaneous evolution in the absence of treatment of any kind, and (2) a valid comparison between groups of treated and untreated patients. Neither of these two requisites can be entirely fulfilled. The course of untreated neurosyphilis is imperfectly understood, and there is available no group of untreated patients upon which to base a valid comparison. Moreover, there are few objective measures of "improvement" upon which penicillin can be compared with older forms of treatment.

The problem of evaluating the results of therapy in neurosyphilis is not new. It was well recognized by Wagner-Jauregg and his associates as they sought to assess the results of malarial therapy. Years of study convinced them that the efficacy of treatment in neurosyphilis should be determined solely by the response of the cerebrospinal fluid, and not at all by the clinical data, the proper interpretation of the latter being a matter of extraordinary difficulty. In the spinal fluid, the cell count and total protein content appeared to be of greatest significance, for in their experience, clinical progression rarely was observed when these two tests were normal.

Thus the concept of spinal fluid "activity" evolved, so ably championed by Dattner, Thomas and Wexler[31] as the only satisfactory expression of the adequacy of treatment in neurosyphilis. Briefly expressed, the "Dattner-Thomas concept" is, that if the spinal fluid cell count and protein become and remain normal following treatment, the active process in the central nervous system has been rendered inactive and non-progressive, regardless of whether there has been any manifest clinical improvement. Such patients, they believe, need not be re-treated. Contrariwise, if treatment fails to reduce the spinal fluid cell count and protein content to normal, or if, having once become normal, one or both of these tests again become abnormal, the process within the central nervous system is considered to be "active." The patient, thus potentially subject to progression or relapse, requires further treatment.

Effect of Penicillin upon Cerebrospinal Fluid Abnormalities. Therapy with penicillin results in improvement in the spinal fluid

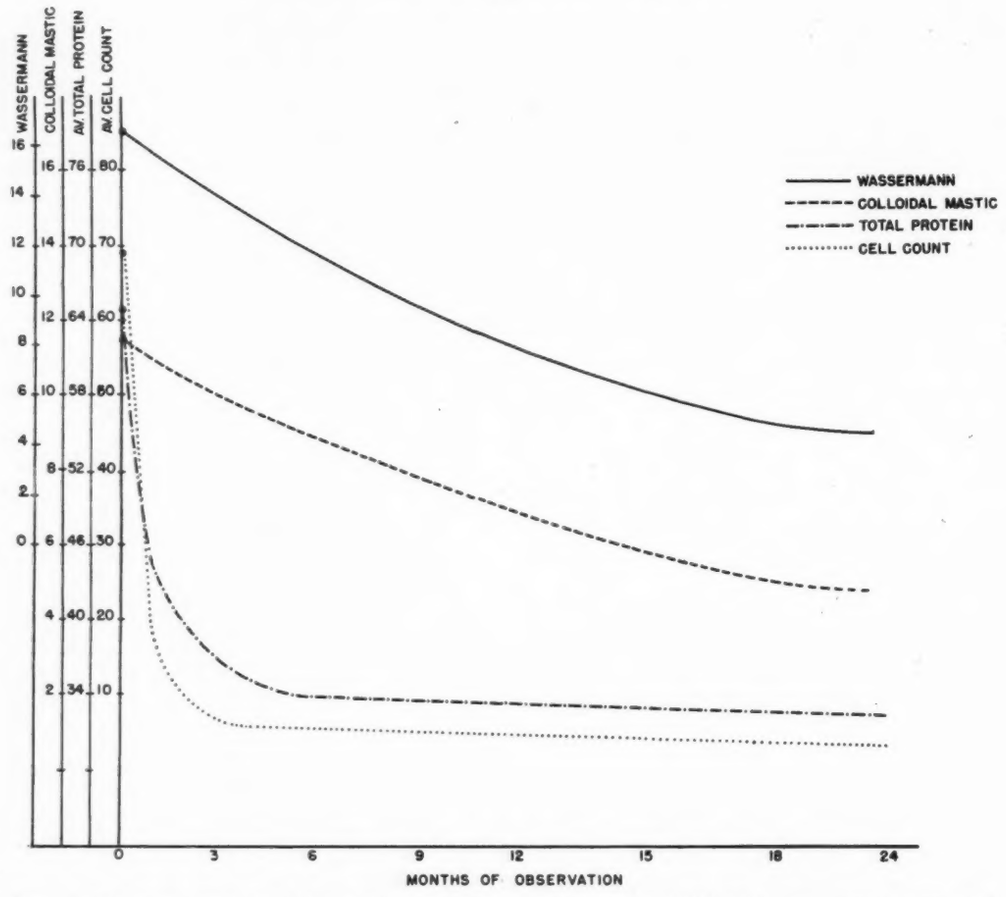


FIG. 2. Changes in spinal fluid abnormalities (all neurosyphilis) following treatment with penicillin alone.

abnormalities of neurosyphilis. This improvement is observed in a high proportion of patients treated, the immediate effect being approximately equally favorable regardless of the type of neurosyphilis.* It has been generally well sustained, at least during the limited period of observation so far available.

The changes in the spinal fluid follow a fairly regular pattern. (Fig. 2.) Elevated cell counts and total protein determinations become normal promptly, usually within a few weeks. This is followed by far more gradual but equally well sustained improvement in the results of colloidal tests and in the Wassermann titer.

Thus, as a result of penicillin therapy the evidences of "activity" rapidly and almost invariably disappear from the cerebrospinal fluid. Not in all cases, however, does the fluid remain inactive. In the series of patients at the Johns Hopkins Hospital, spinal fluid relapse six or more months after treatment has occurred in approximately 7 per cent of those who have been under observation for at least that period. Reactivation of the spinal fluid has been noted more frequently among those with symptomatic (usually parenchymatous) neurosyphilis (9.4 per cent) than among those with asymptomatic involvement of the neuraxis (4.4 per cent).

Asymptomatic Neurosyphilis. In patients whose only evidence of neurosyphilis is a positive spinal fluid, the results of therapy can be adjudged only by: (1) the post-

* With the possible notable exception of Erb's spinal spastic paraplegia.

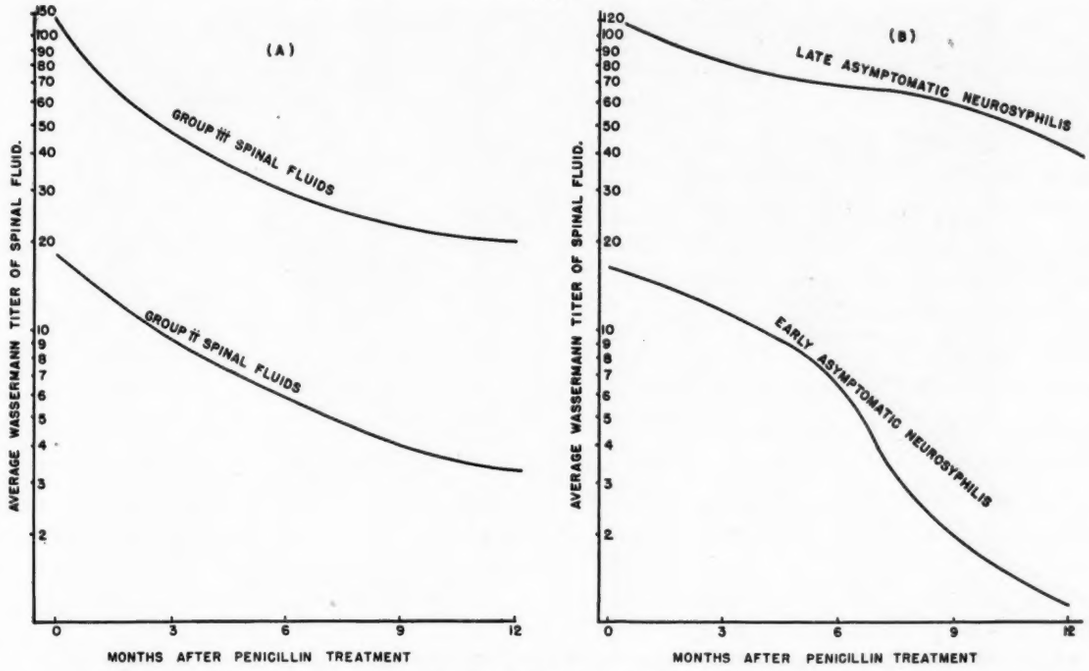


FIG. 3. Average spinal fluid Wassermann titer (arbitrary units)[32] following penicillin therapy, to show the influence of; (A) degree of pre-treatment abnormalities and (B) duration of syphilitic infection. JHH data, smoothed curves.

treatment response of the spinal fluid, and (2) the incidence of progression to clinical neurosyphilis.

The early effect of penicillin upon the spinal fluid has been distinctly encouraging. Moore and Mohr,[32] who recently summarized this clinic's first two years' experience, believe ". . . that penicillin exerts a profoundly favorable effect on spinal fluid abnormalities in early and late asymptomatic neurosyphilis; that this is manifest, in order of promptitude and extent, on cell count, protein content, colloidal test, and, last of all, on the complement fixation (Wassermann) reaction. . . . Within the brief time limits of this study [average duration of observation, 9 months], and keeping in mind the small number of cases involved [91], spinal fluid normality, once achieved, seems usually to be stable."

In asymptomatic neurosyphilis, the *rapidity* with which the spinal fluid becomes normal following penicillin therapy is dependent upon two factors: the degree of the pre-treatment abnormalities, and the duration of the syphilitic infection. (Fig. 3.) Lesser degrees of abnormality and those occurring within the first two years of syphilitic infection disappear rapidly; those more extensive and of longer duration improve slowly over a period of years.

The ultimate result in terms of clinical progression will not be known for many years. If, however, the Dattner-Thomas concept is valid for asymptomatic neurosyphilis, and if the favorable spinal fluid responses thus far noted, sustained, the incidence of clinical neurosyphilis developing in this group of patients should be low.

Effect of Penicillin upon the Clinical Manifestations of Neurosyphilis. However great may be the difficulties in evaluating clinically the results of penicillin therapy in symptomatic neurosyphilis, it is desirable to attempt an over-all approximation. Surely the patient is more interested in how much relief he may expect from his lightning pains or from his mental disturbance than in the cell count of his spinal fluid.

To this end, an attempt has been made to determine from the Johns Hopkins Hospital material what proportion of patients with various forms of neurosyphilis are considered to have been "improved" as a result of penicillin therapy. Details may be found in the several recent reports from this clinic,[33,34,35,36] which summarize the early experiences with penicillin in various forms of neurosyphilis.

Sufficient material has been studied to allow a preliminary estimate of the results in acute syphilitic meningitis, general paresis (including taboparesis), tabes dorsalis, and Erb's spinal spastic paraplegia. (Table II.)

TABLE II
EARLY RESULTS OF THERAPY WITH PENICILLIN ALONE IN CERTAIN FORMS OF NEUROSYPHILIS

	"Improved" Per Cent	No Change or Worse Per Cent
Acute syphilitic meningitis[33]	100	0
Paresis and taboparesis[34]	46	54
Tabes dorsalis[35]	37	63
Erb's spinal spastic paraplegia[36]	0	100

No significant conclusions can yet be drawn in respect to diffuse meningovascular neurosyphilis, syphilitic epilepsy, primary optic atrophy or nerve deafness, although a few patients in each of these categories have been treated.

It is apparent from Table II that the results of penicillin therapy in acute syphilitic meningitis are excellent, but in parenchymatous neurosyphilis the results are not outstandingly favorable. Such improvement as occurred was attained, however, without subjecting the patient to the considerable dangers inherent in fever therapy.*

* In expert hands, the mortality rate from malarial therapy is approximately 1 per cent, from mechanical fever, as high or higher. The percentage of deaths due to fever treatment is inversely proportional to the care used in selecting patients for this rigorous form of therapy and the skill and experience of the attending physician.

There are sound reasons for combining fever with penicillin in the treatment of neurosyphilis. The combination of two effective forms of treatment might be expected to be superior to either alone. Moreover, the spirocheticidal activity of penicillin is known[37] to be enhanced at fever temperatures.

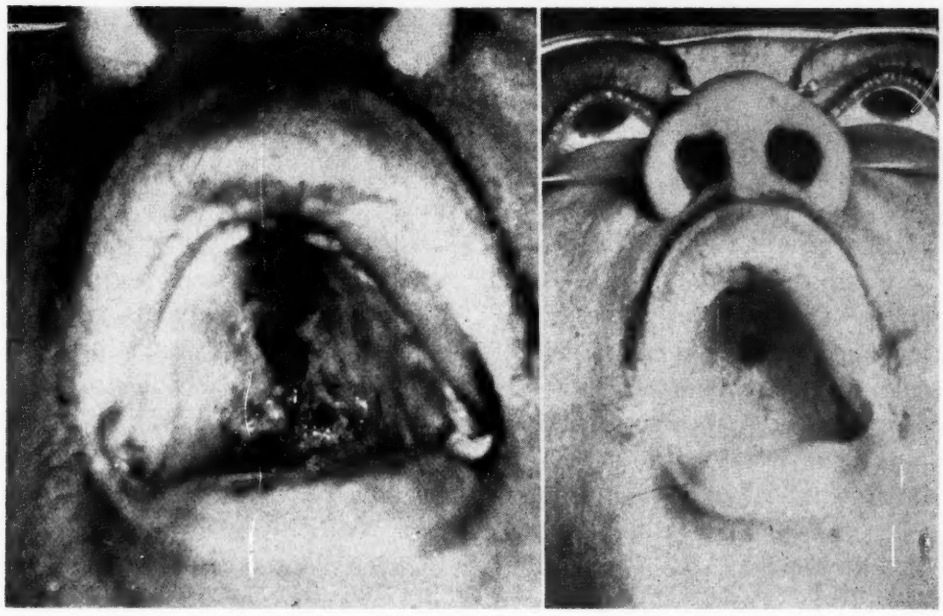
The concurrent administration of penicillin with malarial fever therapy appears, from the experience with general paresis,[34] to offer the patient with late parenchymatous neurosyphilis the greatest promise of a favorable outcome. It is the treatment of choice, therefore, in those forms of neurosyphilis which carry a serious risk to life or vital bodily function: paresis and taboparesis, primary optic atrophy and nerve deafness (in late acquired or congenital syphilis).

For the various syndromes of neurosyphilis, the initial treatment of choice, in the light of information now available, is as shown in Table III.

TABLE III
INITIAL TREATMENT OF CHOICE IN THE VARIOUS SYNDROMES OF NEUROSYPHILIS

Penicillin Alone	Fever Plus Penicillin
Acute syphilitic meningitis	General paresis and taboparesis
Early asymptomatic neurosyphilis	Primary optic atrophy
	Nerve deafness (in late acquired or congenital syphilis)
Late asymptomatic neurosyphilis —Group II —Group III → (?)	
Diffuse meningovascular neurosyphilis —Group II —Group III → (?)	
Tabes dorsalis → (?)	
	Erb's spinal spastic paraplegia

The therapeutic problem in tabes dorsalis and in Erb's spinal spastic paraplegia requires further consideration. In each, the outlook ultimately is for distressingly chronic invalidism. Since the evolution of these con-



A B

FIG. 4. A, gumma of the palate before and B after treatment with penicillin (Dexter and Tucker[39]).

ditions is gradual, with no immediate threat to life or vital bodily function, and since these patients frequently are in such poor general physical condition as to be poor fever therapy risks, it is not unreasonable first to try a form of therapy (e.g., penicillin) which is completely safe, provided there is any reasonable prospect that such therapy may be beneficial. In tabes dorsalis there is such a prospect, but in Erb's spastic paraplegia there appears not to be any.

In any form of neurosyphilis in which penicillin is given as the initial course of treatment, the outcome should be carefully reviewed within six months. If there has been no improvement within that length of time, none may be expected. Re-treatment, usually with malaria (plus penicillin ?) may then be indicated, especially if there is evidence of "activity" in the cerebrospinal fluid.

PENICILLIN IN THE TREATMENT OF OTHER MANIFESTATIONS OF SYPHILIS

Benign Late Syphilis. The healing of[38] the lesions of benign late syphilis affords a most convincing demonstration of the value of penicillin in the treatment of syphilis. Dexter and Tucker,[39] who have studied twenty-one patients with benign late gummatous syphilis in this clinic, report entirely favorable results. In eighteen cases, cutaneous, mucocutaneous or mucosal gummas were present; four of the patients had osseous lesions, and two, gummas of the liver. In these patients the clinical response was uniformly favorable. Cutaneous and mucosal gummas underwent rapid and progressive improvement (Fig. 4) after penicillin therapy, there being only one incipient relapse and one treatment failure in the entire group. The lesions of both of these two patients healed completely following a second and more intensive course of penicillin. Late syphilitic lesions of the skeleton and of the liver appeared to respond favorably to penicillin.

Cardiovascular Syphilis. Evaluation of the usefulness of any therapeutic agent in cardiovascular syphilis involves many years of post-treatment observation. There is, therefore, little information as to the results of penicillin in this important late manifesta-

tion of the disease. We have observed in a few patients some amelioration of the presenting symptoms (precordial pain, dyspnea) following treatment with penicillin. How much of this symptomatic improvement may have been due to hospitalization, bed rest and sedation is difficult to assess.

Caution has been urged[40] in the use of large doses of penicillin in the presence of cardiovascular syphilis in view of possible complications from therapeutic shock. This reaction has not been a serious problem in the limited series of patients coming under our own surveillance.

Latent Syphilis. In the treatment of latent syphilis, the purpose is to prevent the development of late manifestations of the disease. How adequately this can be accomplished with penicillin will not be known for several decades.

The only rationale for treating patients with latent syphilis with penicillin is by analogy. Since the drug possesses spirocheticidal action, and since it promotes the healing of manifest lesions, it is not unreasonable to expect that it *may* avert late complications if given at a time when the infection is clinically latent.

It is obvious, however, that treatment with penicillin offers nothing to those whose serologic test remains positive following adequate[41] metal chemotherapy. To subject this group of patients to further therapy of any kind is to kindle false hopes and to waste time, money and effort.

Early Congenital Syphilis. In infants with congenital syphilis, penicillin appears to be at least as effective* as in early acquired syphilis in adults.[42,43,44] There obtain the same therapeutic considerations, especially in regard to time-dose relationships, although the total penicillin dosage and the size of each injection may be reduced in proportion to the body weight.

Infants with early congenital syphilis often are seriously ill. To add to their already precarious condition, therapy which in itself may be toxic, is highly undesirable. To the extent that penicillin is almost completely devoid of untoward reactions (save alone Herxheimer effects, which only occasionally appear to constitute any serious hazard), it is preferable to older forms of therapy.

There is the additional and highly important consideration of proper pediatric care, with especial attention to adequate hydration and nutrition, and the recognition and treatment of intercurrent infections.

Syphilis in Pregnant Women. In the prevention of prenatal syphilis through treatment of pregnant women with syphilis, penicillin has been highly efficacious.[45] Here it may well be, as Goodwin and Moore[46] suggest, the therapy of choice.

Penicillin readily passes the placental barrier[47] and its spirocheticidal action thus is available to the fetus *in utero*. It appears, despite the contention of some,[48,45] not to provoke uterine contractions and not to precipitate labor.[49] No abortifacient effect of the drug has been apparent in the group of patients treated in this clinic.

The outlook for a non-syphilitic child following penicillin therapy during pregnancy is excellent. Even among those mothers whose syphilitic infection has been recently acquired, and in whom the risk to the child is great,[50] there have been remarkably few treatment failures. Because of the possibility of redissemination of organisms in the course of an infectious relapse, frequent post-treatment observations throughout the remainder of pregnancy are imperative.

* The incidence of infectious mucocutaneous relapse thus far has been significantly lower in infants with early congenital syphilis than in adults with early acquired syphilis.

SUMMARY

In penicillin there is added to the armamentarium of the syphilotherapist a drug

which is of negligible toxicity, readily administered, but with definite limitations in therapeutic effectiveness. It is far from being the ideal form of treatment; yet it is more than a fad. It has, for the present at least, a place in the treatment of syphilis as the most desirable form of therapy presently available for certain of the protean manifestations of this disease and as an adjunct to older methods in others.

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Combined Staff Clinics

Rheumatoid Arthritis

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. CHARLES RAGAN: We would like to discuss a group of diseases which, while very different in some respects, have certain important characteristics in common. This group includes serum sickness, rheumatic fever, lupus erythematosus disseminatus, periarteritis nodosa, rheumatoid arthritis and scleroderma. It is now the fashion to classify these diseases together as disorders of the mesenchyme because they all show pathological changes in connective tissue, with clinical signs usually centering upon the joints and contiguous tendon sheaths, but with microscopic evidence of changes in muscle tissue, the subendothelial tissue of blood vessels and the endocardium, and the connective tissue of the myocardium.

Clinically, too, there is considerable overlapping. For example, it may be difficult to tell whether a given patient has rheumatic fever, rheumatoid arthritis or lupus erythematosus disseminatus. The following cases illustrate some of these points.

The first patient is Mrs. S. I believe you can all see that she has typical fusiform fingers with some limitation of motion of her wrists. The onset of her disease was fairly acute, in January, 1946. She came to us in June, 1946, after rather ineffective treatment. At that time—in June—she was in a wheelchair, confined to her home with flexion deformities of both elbows and both knees. She had a moderate hypochromic anemia. Her blood showed an elevated sedimentation rate and gave a positive agglutination test with group A hemolytic streptococci. We wish to show her as a patient with rheumatoid arthritis in a remission. She has been treated with whole blood transfusions, gold and curare. At the present time she has no flexion deformities, she is able to do her own housework and drives a car.

The second patient is Kathie P., who is now nine years old. She has been sick since 1943. In December, 1943, she had a sore throat followed in two weeks by polyarthritis. At the time she was in another hospital where she had definite pericarditis with effusion. She was first seen in the Babies Hospital in June, 1944, by which time she had developed flexion deformities of both wrists and both knees, and had by *x*-ray loss of joint space in both wrists. Throughout this period she had episodes of fever up to 105°F., which sometimes responded to salicylates and sometimes did not. In 1945 and 1946, she was in the hospital on three or four occasions and at the present time the disease process is still active, with an elevated sedimentation rate and some flexion deformities.

Kathie is to us an example of what is called Still's disease, which is essentially rheumatoid arthritis in childhood. In this age group you see the greatest interrelation between rheumatic fever and rheumatoid arthritis.

The third patient recently came to autopsy. In 1936, two weeks after delivery, she developed polyarthritis with pericarditis. In 1936, 1937, 1938 and 1939, she was

seen at various times at another hospital with episodes of fever. She had several attacks of pleurisy and two bouts of pneumonia. In 1939, while in the hospital, she was observed to have a definite "butterfly" rash on the face. In 1941, she developed ankylosis of the wrists with persistent joint pain and subluxations of the proximal phalangeal joints. In 1943 and 1944, she received some chrysotherapy at the Presbyterian Hospital, and in 1945 she received Bogomolets' serum, all without benefit. In 1946, she was given adequate chrysotherapy, again with no improvement, and she was transfused with whole blood. In August, 1946, she was admitted to Presbyterian Hospital in cholemia and died. I have a picture of her showing the "butterfly" rash. Another picture shows her hands, which are as characteristic of rheumatoid arthritis as any we have seen. A biopsy of the gastrocnemius muscle in 1945 showed a small perineural lymphocytic nodule and at autopsy the characteristic lesions of lupus erythematosus disseminatus were found to be widespread.

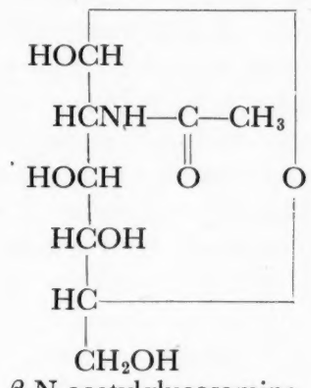
These cases illustrate the clinical and pathological overlapping in the diseases which we would like to consider as a group. We are not clear about the pathogenesis of any of these diseases. Most of the work done in this field in the past has been in the nature of clinical classification. Today we are not concerned so much with classification as with an attempt to clarify the common denominator of the whole group, namely, the pathological lesion located in the mesenchymal or connective tissue.

We might begin our discussion with a summary of recent progress in the chemistry of connective tissue. Dr. Karl Meyer, who has contributed so much to our understanding of the mucopolysaccharides and mucoproteins, is here to present this phase of the subject.

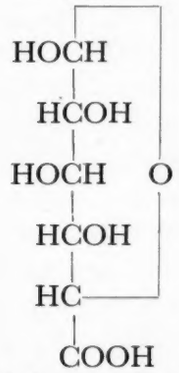
DR. KARL MEYER: Connective tissue is composed of two major structural components, the fibrous elements and the cement substances. The two components belong to quite different classes of chemical substances, the fibrous elements being denatured, insoluble, fibrous proteins of very high molecular weight; whereas the cement substances are compounds or complexes of protein with highly polymerized mucopolysaccharide acids.

The fibrous elements fall into three main groups histologically: collagenous fibers, reticulin fibers and elastic fibers. Collagenous and reticulin fibers are said to be identical in origin and probably have the same chemical structure. The differentiating feature of the two, namely, the silver impregnation of the reticulin fibers, is attributed to closer packing of the fibrils but may, however, be due to a higher concentration of strongly reducing groups in the polysaccharides of the cement substances, as compared with collagen fibers. Collagen and elastic fibers both have a high glycine and proline content but differ in their content of other amino acids. Study by *x*-ray and electron microscopy of collagen fibers in tendon, loose connective tissue, skin and cornea has revealed a fine crystalline structure of the constituent fibrils, with alternating bands of higher and lower density spaced at regular distances from each other. By heating in aqueous solution, the crystalline collagen is converted into soluble and amorphous gelatin. Rat-tail tendon and all embryonic collagen fibers are soluble in salt-free dilute acids, forming extremely viscous solutions, as Nageotte has shown; while all other collagen fibers are insoluble in these solvents. The cause of this difference in solubility is unknown. On addition of salt or on neutralization, the proteins in these solutions precipitate as fibers which possess the same fine structure as the native fibers. Native adult collagen fibers are digested by pro-

teolytic enzymes at a very low rate, comparable to the digestion of other fibrous proteins, like keratin.



β-N-acetylglucosamine



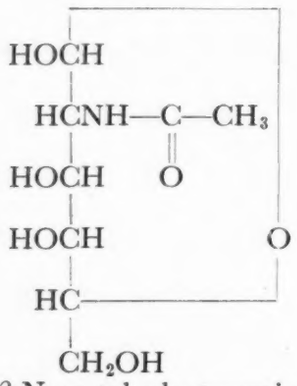
β-*d*-glucuronic acid

The interfibrillar or cement substances seem to be of considerable importance in the mechanism of rheumatic diseases, and will be discussed in some detail. According to the fundamental studies of Klinge, the primary lesions in rheumatic fever and rheumatoid arthritis are located in the interfibrillar spaces, while the swelling, fragmentation and finally lysis of the fibers is a secondary phenomenon. The chemical nature of the proteins of the cement substances is unknown. The mucopolysaccharides which are more or less loosely bound to the proteins have been studied more extensively. Up to the present time four mucopolysaccharides have been identified as components of cement substances, (1) hyaluronic acid, (2) hyaluronosulfuric acid, which has been found only in cornea, (3) chondroitin sulfuric acid, and (4) the sulfuric acid ester occurring in amyloid tissue. The latter may be a component of normal mesodermal tissue which accumulates in excessive amounts in amyloid disease. It appears to be derived from heparin.

Hyaluronic acid is a polymer of a disaccharide composed of N-acetyl glucosamine and glucuronic acid. Its exact structure, like that of other mucopolysaccharide acids, is still unknown. The molecular weight of hyaluronic acid varies according to the source from which it is obtained; it has been estimated as between 200,000 and 500,000, and may be even higher. Hyaluronic acid occurs in vitreous and aqueous humor, in Wharton's jelly of umbilical cord, in synovial fluid, in skin and in some mesodermal tumors. In micro-organisms, it has been found only in group A and C hemolytic streptococci, when the organisms are in the mucoid phase. Mucoid phase and hyaluronate production have been correlated in some types with invasiveness of the organisms and with their resistance to phagocytosis and to destruction by whole blood. All attempts to produce antibodies against hyaluronic acid have failed.

Hyaluronic acid is depolymerized and hydrolyzed by specific enzymes called hyaluronidases, which occur in micro-organisms such as pneumococci, streptococci, staphylococci and in gas gangrene-producing organisms. Among animal sources the enzyme has been found in snake venoms, in the leech, and (in very high concentration) in the mature mammalian testis, or, more specifically, in spermatozoa. In the latter, the enzyme facilitates the depolymerization of the mucoid ground substance of the cumulus cells of the ovum, thus preparing it for fertilization. The greatest store of hyaluronidase in the mammalian body seems to be the skin where, however, it appears to be largely in an inactive form.

A very interesting property of hyaluronidases is their effect on dermal diffusion, the so-called spreading reaction of Duran-Reynals. This reaction usually is carried out in rabbits or in guinea pigs, but also has been observed in man. On intradermal injection of an indicator together with suitable concentrations of enzyme, the indicator diffuses in the skin over a wide area as compared to the localized bleb in control injections of indicator without hyaluronidase. The spreading reaction has been demonstrated also in the wall of the stomach and intestine, in muscle, fasciae and tendon. However, in contrast to skin, no hyaluronic acid has been isolated thus far from these sources.



β-N-acetylgalactosamine

Chondroitin sulfuric acid has a molecular weight similar to that of hyaluronic acid. It is a polymer of a disaccharide composed of equimolar concentrations of N-acetylgalactosamine, glucuronic acid and sulfuric acid, the latter apparently in the C_6 position of the galactosamine. Chondroitin sulfuric acid has been isolated from hyaline cartilage, from umbilical cord and from skin. A fraction recently isolated from calves' tendon is probably also chondroitin sulfate. It should be noted that two tissues contain hyaluronate and chondroitin sulfate in about equal concentrations, namely, skin and umbilical cord. Synovial fluid, vitreous humor and the tumor fluids contain only hyaluronate, while cartilage contains only chondroitin sulfate.

Chondroitin sulfates probably are mixtures of similar but not identical compounds, some of which are hydrolyzed by hyaluronidases or by enzymes associated with hyaluronidases. The spreading effect in some tissues thus may be due to the hydrolysis of chondroitin sulfate rather than to that of hyaluronate. The metachromasia of some dyes (such as toluidine blue) shown by connective tissue and cartilage appears to be caused by chondroitin sulfate. Hyaluronate does not seem to be stained by any of the usual methods.

The known data of the chemistry of the connective tissue, when considered in relation to what has been learned by histological and tissue culture studies, suggest the following mechanisms in the development of connective tissue: The young, growing fibroblasts secrete hyaluronic acid, which is followed by the secretion of chondroitin sulfate and of a precursor of collagen, the latter a non-fibrous and soluble protein. By local acidification in the immediate neighborhood of the fibroblasts, the precursor is denatured by the polysaccharides, the latter acting as anionic detergents rolling up the peptide chains along the acidic groups of the fibrous polysaccharide molecules. Most of the hyaluronate is removed enzymatically, leaving the more firmly bound chondroitin sulfates as a network on the surface of the fibers. The latter by crosslinking grows into the mature insoluble fibers.

The pathological chemistry of connective tissue is still in an embryonal state. However, some insight into this field might be gained by recent studies (in collaboration with Dr. Ragan) on synovial fluid which embryologically, and to some extent physiologically, is related to connective tissue. The concentration of hyaluronate was measured by a turbidimetric method in

normal and pathological synovial fluids. Pathological fluids in this reaction appear as a stable colloidal turbidity, while normal fluids of man and cattle precipitate as a fibrous clot containing the polysaccharide. This clot formation is prevented by one hundredth of a unit of hyaluronidase, an amount too small to decrease measurably the hyaluronate concentration. With normal vitreous humor a colloidal precipitate is obtained, while in aqueous humor 95 per cent of the total hyaluronate is found in depolymerized, non-precipitable form. This depolymerization is due to the co-presence of hyaluronidase, which was demonstrated in a concentration of about 0.4 u/cc. in ocular fluid.

In synovial fluid no measurable amount of hyaluronidase could be demonstrated, unless the colloidal precipitation is taken as an indication of the presence of the enzyme in low concentration. The viscosities of over thirty synovial fluids examined were not directly proportional to the hyaluronate concentrations, the viscosities being higher and the hyaluronate concentrations lower in normal fluids as compared with pathological synovial fluids, obtained chiefly from cases of rheumatoid arthritis. In view of the increased volume of fluid in these pathological joints, they contain a considerably larger total amount of hyaluronic acid. In other words, the injured synovial cells apparently produce an excess of the acid, which may be followed by a compensatory increase of hyaluronidase, the source of which is undetermined.

Similar changes may occur in other mesenchymal tissue spaces leading to an increase in interfibrillar cement substances. Such an increased concentration of highly viscous material would presumably slow down metabolic processes.

DR. RALPH H. BOOTS: What is the relation of "mucin" and "mucinase" to hyaluronic acid and hyaluronidase?

DR. MEYER: The term "mucin" in classical usage means any viscous secretion which on acidification with dilute acetic acid gives a ropy precipitate. Synovial fluid, which contains hyaluronic acid in considerable concentration, shows this phenomenon and is therefore said to contain "mucin." However, the "mucin" precipitated in this way is an artefact since the native hyaluronate of synovial fluid is not bound to protein, as shown by electroploretic studies. Vitreous humor and some cystic tumor fluids also contain hyaluronic acid but often fail to give a precipiate with acid. The low protein or high salt content of these fluids is responsible for their failure to precipitate. Gastric mucin contains two mucopolysaccharides which are unrelated to hyaluronic acid. Salivary mucin, too, contains no hyaluronic acid.

The term "mucinase" has also been used to denote different enzymatic reactions, such as depolymerization of the mucopolysaccharide of synovial fluid (hyaluronic acid), the liquefaction of salivary mucus, etc.

I think it would be best either to drop the ambiguous terms "mucin" and "mucinase" or to use them only in a non-chemical sense.

STUDENT: Vitamin C has been shown by Wolbach to be essential for the growth of connective tissue. How does vitamin C fit into your concept of connective tissue development?

DR. MEYER: There is no definite information on the rôle of ascorbic acid in the genesis of the fiber. The sensitivity of some of the chondroitin sulfates to alkali and oxygen, and their ultraviolet spectra, suggest that ascorbic acid or a derivative of it may actually be a component of chondroitin sulfate, perhaps replacing some of the glucuronic acid units.

DR. RAGAN: We now would like to turn to one of the group, rheumatoid arthritis.

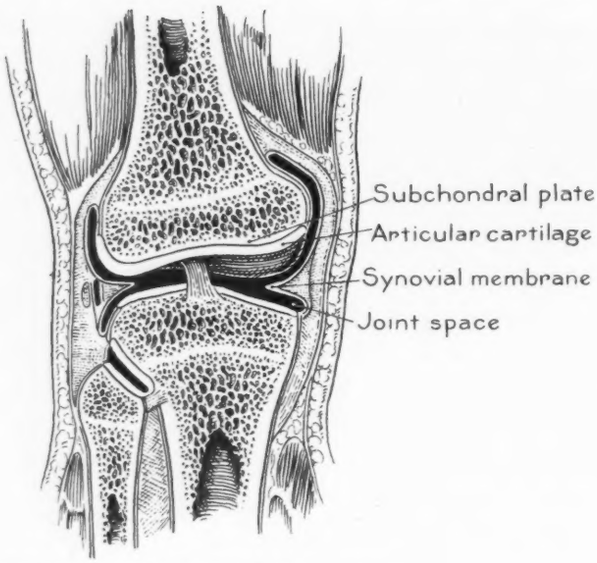


DIAGRAM OF DIARTHRODIAL JOINT

FIG. 1.—(After Callender.)

This is a severe progressive disease. It is of great social and economic import and various public health surveys have shown that chronic arthritis is a major cause of suffering and economic loss. Until recently rheumatoid arthritis was considered a disease purely of the joints. In the past ten years, however, evidence has accumulated which indicates that the disease is more generalized. Dr. Flynn of the Department of Pathology has been asked to discuss the morphological changes which are found.

DR. JOSEPH F. FLYNN: As has been stressed by previous workers, rheumatoid arthritis is indeed a protean disease, a disease whose clinical course may be characterized by remissions and exacerbations, a disease whose onset may be acute or insidious, a disease which may attack the individual at any age, a disease which may progress with incredible rapidity producing what has been aptly called the rheumatoid derelict, or again a disease which after a brief course may end abruptly, disappear and never return again.

The systemic pathology of this disease is almost as varied as are its clinical manifestations. By "systemic pathology" I mean the lesions of the kidney, the bladder, the lymph nodes, the eye, etc. There are, however, a number of locations in which the changes are remarkably constant and it is on these that I will chiefly dwell. These locations are the joints, the nodules of the subcutaneous tissue, the nerves and the muscles.

Joint Pathology. Before demonstrating the pathology of the rheumatoid joint, I will review very briefly the anatomy of the diarthrodial joint. The anatomy of diarthrodial joints is essentially the same regardless of their location, whether the hand, wrist, foot, shoulder, knee, etc. The bones constituting the joint are covered by a layer of hyaline cartilage, called the articular cartilage. (Fig. 1.) It rests on a thin layer of dense bone known as the subchondral plate. You will recall that the joint cavity is lined by a continuous membrane, the stratum synovale or the synovial membrane. This is a layer of specialized connective tissue. It begins at the margin of the articular cartilage, covers the intra-articular portions of the bones and is reflected on the capsule to end at the margin of the opposite articular cartilage. Microscopically, the surface of the synovial membrane is thrown up into a number of tiny villous projections. This gives the membrane great flexibility, permitting it to be stretched for a considerable distance.

The synovial membrane is made up of collagen in which are imbedded the synovial cells—the modified fibroblasts. Intermixed with connective tissue, are a number of blood vessels, a few lymphatics, a few nerves and a few wandering cells. The structure of synovial membrane is essentially the same regardless of its location. However, the tissue on which it rests may vary.

The primary lesion of rheumatoid arthritis is an inflammation of the synovial membrane. It becomes enormously thickened by edema, hyperemia and inflammatory cell infiltration. As a result of

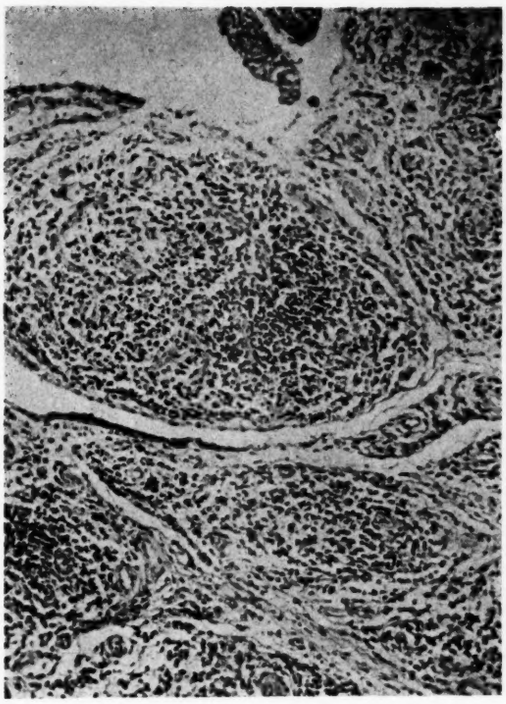


FIG. 2. Subacute villous synovitis from a case of severe rheumatoid arthritis. The stratum synovale is enormously widened by edema, hyperemia and inflammatory cell infiltration.

edema there is often seepage of fluid out into the joint and this together with the increased activity of the synovial cells accounts for the great increase in joint fluid. This increased joint fluid stretches the capsule, often producing pain.

Figure 2 shows the rather typical appearance of the inflamed synovial membrane. Note the enormous widening of the membrane and the exaggeration of the villous projections. In the hypertrophic villi are collections of lymphoid cells. Some years ago an orthopedist, describing the pathology of rheumatoid arthritis, found collections of lymphocytes so arresting that he stated they were absolutely specific for rheumatoid arthritis. This is but another example of the all too frequent attempt to create pathological specificity on the basis of insignificant morphological alterations. Needless to say, there is nothing pathognomonic about it. They are found in a number of conditions.

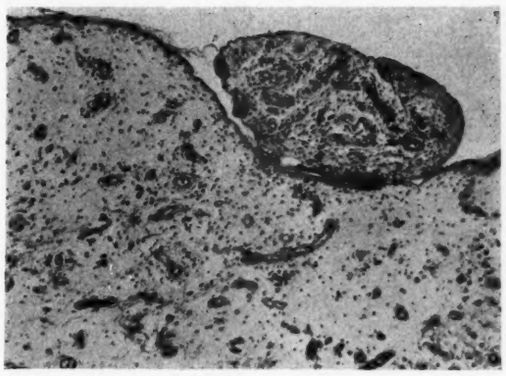


FIG. 3. Subacute villous synovitis with pedunculation of one of the villi. Often these pedunculated villi become necrotic and separate away to form free bodies within the joint. Note the increased vascularity, widening of the tissue spaces and inflammatory cell infiltration.

Often in rheumatoid arthritis the hypertrophic villi become pedunculated as seen in Figure 3. If these pedunculated villi become necrotic, they separate away to form free bodies in the joint space. Large amounts of fibrin are often deposited on the surface of the membrane or in the membrane itself. The fibrin is eventually organized and adhesions may result. In severe cases the inflamed synovial membrane may project into the joint space to form a pannus that creeps across the cartilage, like ivy grows across a wall. As it creeps across, the articular cartilage is destroyed. Now, and now only, excluding osteoporosis and swelling of the soft tissue, does roentogenographic evidence become apparent. This evidence consists first of a narrowing of the joint space due to disintegration of the articular cartilage. In severe cases, often simultaneously with the formation of the pannus, granulation tissue forms just beneath the subchondral plate.

Figure 4 is a section through the distal end of a normal femur. It shows a portion of the articular cartilage, beneath which is the subchondral plate. Below the subchondral plate are narrow spaces normally occupied by fibro-fatty tissue. In severe rheumatoid arthritis granulation tissue is present in the marrow spaces just beneath

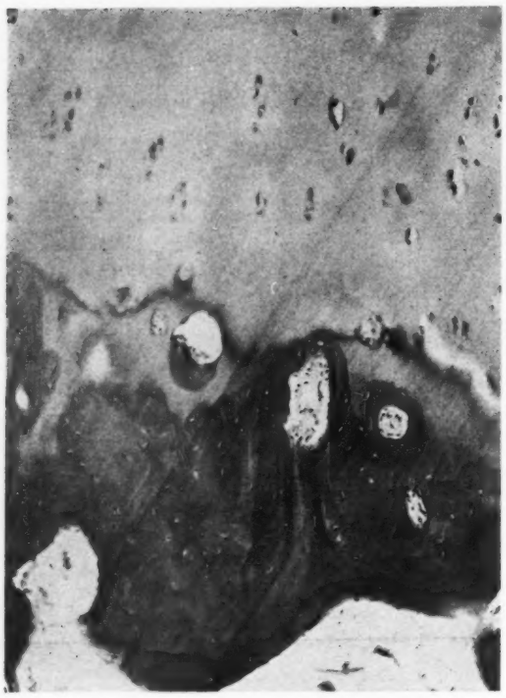


FIG. 4. A section through the distal end of a normal femur. Above is a portion of the articular cartilage, resting on a layer of compact bone called the subchondral plate. Below is the fibro-fatty marrow.

the subchondral plate. The proliferation of the granulation tissue destroys the osseous trabeculae and the subchondral plate. When this occurs the articular cartilage is attacked from above and below, above by the pannus and below by the granulation tissue. If this occurs in both bones, the end result is a bridge of granulation tissue that stretches across the joint space. In time the granulation tissue becomes converted into fibrous tissue, producing a fibrous ankylosis that eventually goes on to bony ankylosis. Figure 5 shows some of these changes. The articular cartilage is degenerated as manifested by its altered staining reaction, the disalignment of the cells and empty lacunae. Above the articular cartilage is a pannus. Below the articular cartilage there is dissolution of the subchondral plate. Near one margin the granulation tissue from below almost reaches the pannus.

Figure 6 is a section from a "burned-out"

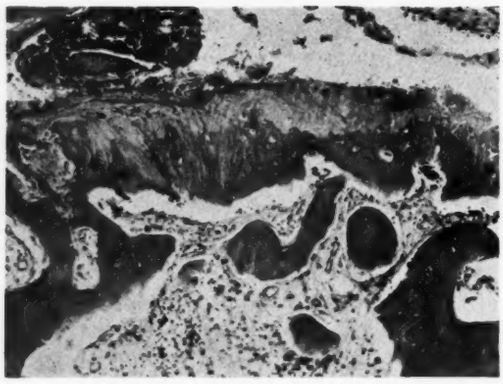


FIG. 5. A photomicrograph of a section through a diarthrodial joint showing marked rheumatoid arthritic changes. Above is the pannus creeping across the articular cartilage. The cartilage is degenerating. Note its altered staining reaction of the cartilage, large lacunae and disorderly arrangement of the cells. Below the articular cartilage, granulation tissue has destroyed the subchondral plate and is replacing the cartilage.

case of rheumatoid arthritis. This patient had an ankylosis of the femur and tibia. Here there is complete destruction of the articular cartilage with replacement by dense connective tissue.

Figure 7 is a roentgenogram of a wrist joint showing severe rheumatoid arthritic changes. Note that the joint spaces of the metacarpals are destroyed. The joint spaces between the metacarpals, radius and ulna are bridged across by osseous tissue. It must be remembered that the entire sequence of events just enumerated does not always occur. In many cases the process simmers along with remissions and exacerbations, without much pannus formation and without much granulation tissue beneath the subchondral plate.

Subcutaneous Nodules. As Bennett and Bauer[1] point out, the nodules of the subcutaneous tissue have received a great deal of attention. These workers have stressed the point that they are probably the most

[1] BENNETT, G. A., ZELLER, J. W. and BAUER, W. Subcutaneous nodules of rheumatoid arthritis and rheumatic fever; pathologic study. *Arch. Path.*, 30: 70–89, 1940.

FIG. 6. A photomicrograph showing the end state of rheumatoid arthritis—fibrous ankylosis. Above is dense connective tissue. The articular cartilage is destroyed as is the subchondral plate. The granulation tissue has disappeared and the marrow spaces are occupied by fibrofatty tissue.

FIG. 7. A roentgenogram of the right hand and forearm showing marked rheumatoid arthritic changes. There is reduction of the joint spaces of the wrist and hand due to destruction of the articular cartilage. A bony ankylosis of the carpal bones has occurred involving all except the pisiform. Punched out areas of periarticular bone destruction are present in the distal end of the metacarpal bones. These are due to proliferating granulation tissue beneath the subchondral plate. There is marked ulnar deviation of the phalanges.

specific lesion of rheumatoid arthritis. The nodules usually measure about 1 to 2 cm. in size. Basically they consist of connective tissue in which are a number of granulomatous lesions. As a rule there are about five granulomatous lesions in the plane of any given section studied. The granulomas are made up of a zone of necrosis, then a zone of inflammatory cell reaction and then a zone of connective tissue. The necrotic tissue is disintegrated collagen. The inflammatory reaction consists of large mononuclear cells. Often multinucleated giant cells are present so that the lesion resembles tuberculosis. Indeed these nodules are sometimes called tuberculosis by the misinformed.

Muscles and Nerves. In 1942, Freund[2] and his associates described what they called a specific, inflammatory nodule involving the perineurium of many nerves in rheumatoid arthritis. In 1945, Freund[3] described similar lesions in the muscles. He called the lesions in the nerves "nodular perineuritis," and in the muscles "polynodular polymyositis."

Figure 8 shows a fairly typical lesion in the perineurium of a nerve, cut longitudinally. Basically the nodule consists primarily of lymphocytes. They may be small, consisting of only a few lymphocytes, or they may be large enough to be seen with the

[2] FREUND, H. A., STEINER, G., LEICHTENTRITT, B. and PRICE, A. E. Peripheral nerve in chronic atrophic arthritis. *Am. J. Path.*, 18: 865–893, 1942.

[3] FREUND, H. A., STEINER G., LEICHTENTRITT, B. and PRICE, A. E. Nodular polymyositis in rheumatoid arthritis. *Science*, 101: 202–203, 1945.

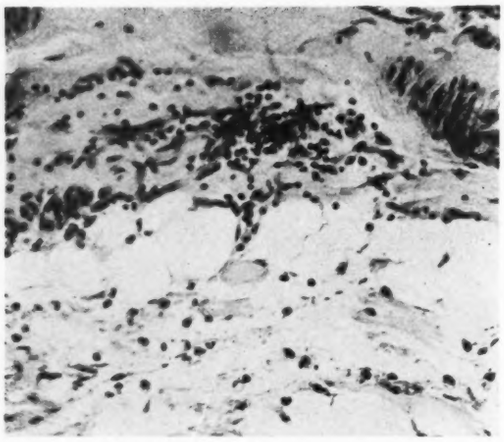


FIG. 8. A photomicrograph showing a nodular perineuritis. Near the top of the photomicrograph is a small nerve cut longitudinally. In the nerve is a dense collection of lymphocytes.

naked eye. Similar lesions[4] are found in disseminated lupus and in dermatomyositis. Neither are the lesions in the muscles specific, since I have seen identical lesions in the atrophic muscles of poliomyelitis.

DR. RAGAN: The etiology of rheumatoid arthritis is unknown. I have asked Dr. Coss to review the present status of our knowledge of the relation of the hemolytic streptococcus to rheumatoid arthritis.

DR. JAMES A. COSS: Various organisms have at one time or another been implicated as the etiologic agent in this group of diseases without confirmation. At the turn of the century Westphal in Germany, and Poynton and Paine in England, directed attention to streptococci as a result of their cultural studies. This interest has been revived periodically by reports, from abroad as well as in this country, to the effect that a definite organism could be isolated from rheumatic lesions. Up to the present time numerous investigators have been unable to confirm these various reports. No one has succeeded in fulfilling Koch's postulates for any etiologic agent reported associated with rheumatoid arthritis.

Certain bits of evidence have served further to implicate the hemolytic streptococcus, however. Todd has described an antistreptolysin test by means of which the titer of this streptococcus antibody can be measured. For practical purposes it is the antistreptolysin-O which is determined. It is elevated following acute hemolytic streptococcus infections, in nephritis, rheumatic fever and occasionally in the early stages of rheumatoid arthritis.

Cecil, Nichols and Stainsby described an agglutination reaction with group A hemolytic streptococci which was found to be positive in a high percentage of patients with rheumatoid arthritis. This was confirmed in our laboratory by Dawson, Olmstead and Boots. Since 1931, we have tested approximately 10,000 blood specimens for streptococcus agglutination. Fifty to 60 per cent of patients with rheumatoid arthritis give a positive streptococcus agglutination test. We have found a positive agglutination in fifty-six patients with diseases other than rheumatoid arthritis. Of these so-called "false" positives, twenty were in the group of the mesenchymal diseases.

In a review of fifty-six cases of juvenile rheumatoid arthritis[5] we have found the median antistreptolysin-0 titer to be 1 to 250, much higher than the normal maximum of 1 to 100 as read in our laboratory. Of all these patients tested, only three had a positive agglutination with group A hemolytic streptococci, as compared with a figure of 55 per cent positive in the adult disease. The absolute significance of such observations as these cannot be estimated until we know more about the agglutination reaction itself. It has recently been shown that the serum of some patients will agglutinate not only group A hemolytic streptococci but also non-specific particulate suspensions, such as unsensitized collodion particles (Wallis[6]). We are trying to clarify some of these points at present.

[4] BAUER, W. Personal communication.

[5] COSS, J. A. and BOOTS, R. H. Juvenile rheumatoid arthritis. *J. Pediat.*, 29: 143, 1946.

[6] WALLIS, A. D. Personal communication.

The streptococcus agglutination reaction probably is a non-specific test which, in our laboratory, has proven a useful tool in the study of arthritis. At times it fails to give a positive result in obvious cases of rheumatoid arthritis, very infrequently it gives false positive results, and the mechanism of the reaction is not clear.

STUDENT: Can rheumatoid arthritis be produced in experimental animals by injection of streptococci?

DR. COSS: Much of the difficulty in studying rheumatic disease has been our failure to reproduce the disorder in experimental animals. Streptococci injected intravenously into rabbits will cause arthritis, myocarditis and endocarditis; however, the lesions are not similar to the lesions seen in human beings. Such arthritis is not migratory, does not recrudesce spontaneously and is not self-perpetuating. In the cardiac lesions many similarities exist, but Aschoff bodies have not been described.

Rothbard produced arthritis in forty-five of fifty-one rats by injection of group A hemolytic streptococci from a case of septicemia and Rigdon was able to produce arthritis in rabbits by intra-articular injection of a staphylococcus toxin. None of these experiments, however, has resulted in an arthritis characteristic of the clinical picture as seen in human beings. Selye[7] produced polyarthritis by treatment with adrenal cortical hormone but the technics necessary to bring about the lesions were quite vigorous.

Spontaneous arthritis has been observed in various animals, notably a polyarthritis of rats first reported and studied by Collier[8] and assumed to be due to a pleuropneumonia organism; also arthritis in swine due to the erysipelothrix (Collins and Goldie[9]), "strangles" in horses, and quite recently an arthritis in swine which seems to be caused by a virus (McNutt[10]). In these instances, and in many others which might be mentioned, it is possible to find as an exciting factor either an infectious agent or a deficiency in some food element, such as exists in the manganese deficiency sometimes responsible for lameness in swine.

DOCTOR: Since you include serum sickness, which has a well established allergic basis, as one of the group, is there any evidence that any of the others in the group has an allergic basis?

DR. COSS: It has been known for years that administration of heterologous serum in small amounts causes arthritis in 10 per cent of the recipients while large amounts cause arthritis in 90 per cent. It is possible to prevent or markedly diminish the arthritic component of serum sickness by the use of salicylates, and this is the one measure which also seems to benefit most victims of the rheumatic diseases.

Because of the implied allergic nature of one end of the spectrum of rheumatic disease (serum sickness), there has been much interest in the report of Klinge (1940) that it was possible to cause arthritis in rabbits by the repeated injection of horse serum. Rich[11] has reported that he was able to cause the lesions of periarteritis nodosa in rabbits also by the injection of horse serum.

Zinsser believed that acute rheumatic fever represented an allergic state for the following reasons: (1) the joint symptoms in anaphylaxis are more or less similar to those seen in articular rheumatism; (2)

[7] SELYE, H. Hormonal production of arthritis. *J. A. M. A.*, 124: 201, 1944.

[8] COLLIER, W. A. and STAVERMAN, G. J. The spontaneous polyarthritis of rats and the syndrome induced by innoculation of human material in these animals. *Ann. Rheumat. Dis.*, 2: 58, 1940.

[9] COLLINS, D. H. and GOLDIE, W. Observations on polyarthritis and on experimental erysipelothrix infection of swine. *J. Path. & Bact.*, 1: 323, 1940.

[10] MCNUTT, S. H., LEITH, T. S. and UNDERBJERG, G. K. An active agent isolated from hogs affected with arthritis. *Am. J. Vet. Research*, 6: 247, 1945.

[11] RICH, A. R. Hypersensitivity in pathogenesis of rheumatic fever and periarteritis nodosa. *Proc. Inst. Med. of Chicago*, 15: 270, 1945.

joint fluid cultures in articular rheumatism are usually sterile; (3) the joint lesions caused by injection of bacteria intravenously into animals are usually sterile; and (4) the sensitiveness of joints in experimental animals seems to some extent to run parallel to general sensitiveness. Against the theory of bacterial allergy in rheumatoid arthritis is the fact that no constant relation has been demonstrated between the organisms found and the skin reactions which the organisms in question afford. The sensitivity of the arthritic patients' skin to the nucleoprotein of strains of streptococci does not follow the course of the disease in all cases. Attempts at patient desensitization have failed. The following criteria of an allergic disease have not been fulfilled, namely, the determination of allergen by skin test or passive transfer of sensitivity, the disappearance of symptoms when the allergen is removed, the reappearance of symptoms on re-exposure to the allergen. If we try to enroll the hemolytic streptococcus as a bacterial allergen causing rheumatoid arthritis, it fails to fulfill the second criterion offered. We gave penicillin over a six months' period to ten arthritic patients in doses large enough to inhibit the hemolytic streptococcus but no change occurred in the course of the disease nor was there a change in the streptococcus agglutination reaction from positive to negative.[12] Similar attempts to eliminate the streptococcus by means of sulfonamides have failed in arthritis.

The Caveltis[13] recently have prepared an antigen from ground-up human heart suspension which was used to coat collodion particles prepared according to the method of Cannon.[14] A positive streptococcus agglutination response with the sera of approximately 75 per cent of rheumatic fever patients was found when tested against this antigen. They previously demonstrated that auto-antibodies to kidney can be produced by immunization of animals with mixtures of group A hemolytic streptococci and kidney of the same species. This work has not as yet been confirmed, but in view of the close relationship of streptococcal infection and rheumatic fever, we are naturally much interested.

DOCTOR: What has been your experience with Bogomolets's serum in the treatment of arthritis?

DR. COSS: The anti-reticular cytotoxic serum, or ACS, which was developed in Russia was said to be of value in the treatment of various conditions including rheumatoid arthritis. Bach[15] treated a group of patients without any appreciable benefit whereupon the originators of the serum said it was of value only in the second or allergic phase of disease. We have treated about thirty patients with this preparation with inconclusive results to date.

DR. RAGAN: It is often difficult to state confidently that such-and-such a patient does have rheumatoid arthritis. To us in the management of the patient, the most important practical problem in diagnosis is to differentiate whether the patient has rheumatoid arthritis or rheumatic fever. The joint symptoms of rheumatic fever are amenable to relatively simple treatment and rarely lead to deformity, whereas the joint manifestations of rheumatoid arthritis are, by and large, progressive and treatment should be so directed that progression is blocked and the deformities which lead to eventual crippling be kept at a minimum.

I would like to mention briefly the use of gold compounds. Gold compounds containing a sulfhydryl group were first used

[12] COSS, J. A., BOOTS, R. H. and LIPMAN, M. O. Prolonged administration of penicillin in arthritis. (In press.)

[13] CAVELTI, P. A. Auto antibodies in rheumatic fever. *Proc. Soc. Exper. Biol. & Med.*, 60: 379, 1945.

[14] CANNON, P. R. and MARSHALL, C. E. An improved serological method for the determination of precipitative titers of antisera. *J. Immunol.*, 38: 365, 1940.

[15] BACH, F. ACS serum in rheumatism. *Ann. Rheumat. Dis.*, 4: 62, 1945.

in the treatment of rheumatoid arthritis in 1927, by Feldt in Germany. Forestier in France used gold extensively but it was not employed in this country until about 1938.

The treatment is purely empirical. The hypotheses upon which Forestier and Feldt based their rationale for treatment have not been substantiated. Much hostility has been raised towards gold because of the severe toxic reactions which are observed following its use.

Between 5 and 10 per cent of the patients with rheumatoid arthritis are unable to tolerate therapeutic amounts of gold because these patients develop a toxic reaction before an adequate amount of gold can be given. Of patients who have received full treatment, an average of 10 to 20 per cent show no improvement, 40 to 60 per cent show striking improvement with one or two courses. Follow-up studies reveal that at least 80 or 90 per cent of these patients relapse within five years, so that the response to gold constitutes a remission of the disease and not a cure.

It might be worth while to say that the relapse is not as severe as the original disease but, again, the response to treatment with gold after relapse is not as dramatic as the response to the first course.

I want to mention again what Dr. Flynn has stressed, namely, that this is a disease in which spontaneous remissions and exacerbations occur, and any form of therapy must be evaluated critically. However, in the experience of the Arthritis Clinic over a period of seventeen years, in which about 2,000 patients with rheumatoid arthritis have been seen, we have not found any therapy other than gold therapy which will consistently and in a high percentage of cases change the course of the disease. Since we believe that a relapse after gold therapy is to be expected, when a patient shows improvement and no toxicity it is our present policy to continue administration of gold on a maintenance schedule.

Gold toxicity affects certain systems: the skin, as manifested by various pruritic lesions, with occasional severe exfoliative rashes; the gastrointestinal tract, with stomatitis or abdominal symptoms; and damage to the hemopoietic and renal systems. The stomatitis and renal damage may be due to overdosage, since these are similar to what is found in bismuth and other heavy metal poisoning, and we believe we can avoid these by smaller doses. The dermatitis cannot be predicted in any way. We do not know when to expect it. It may come early and it may come three to four months after the last gold has been given.

There is some encouragement in the use of BAL (British AntiLewisite) in the early treatment of toxicity but at the present time it is too early to evaluate these results. We can say definitely that with the administration of BAL there is a significant increase in excretion of gold in the urine.

The dosage schedule of gold compounds which we now employ is as follows: We use Solganol-B Oleosum, which is aurothioglucose. We start with small doses, 10 mg., and then increase to 25 mg. and, if tolerated, to 50 mg. at weekly intervals, and continue at 50 mg. weekly until the patient has received 1.0 Gm. of the compound. If the patient has shown improvement and has had no untoward toxic effect, the gold is continued, 50 mg. every two or three weeks. At the onset of any toxic manifestation, the gold is discontinued. Depending on the severity of the toxic reaction, gold may not be given again or it may be resumed in smaller amounts. We have not had the courage to resume gold following severe toxic reactions, such as a rash, so we cannot say that once a patient has had a severe reaction that patient is permanently sensitized to gold. It would appear that a patient who has had the disease for more

than two years is more likely to develop a toxic reaction than an early case. The toxic reactions can persist for long periods. Several of the dermatitides have lasted for over two years. We have had two deaths (in over 400 gold-treated cases) which could be attributed directly to gold, one due to aplastic anemia and the other to thrombocytopenic purpura.

Patients with rheumatoid arthritis and psoriasis respond less favorably to gold than those who do not have associated psoriasis. Rheumatoid arthritis of the spine, or ankylosing spondylitis of the Marie-Strumpell type, does not respond at all to chrysotherapy.

DR. PUTNAM C. LLOYD: Is there anything known of the mechanism of the action of gold in rheumatoid arthritis?

DR. RAGAN: The original work done by Feldt was begun because of the clinical similarity between rheumatoid arthritis and tuberculosis. In 1914, gold was found to be bacteriostatic and recently Dawson and Hobby showed that gold was bacteriostatic against group A hemolytic streptococci. Until the pathogenesis of the disease is more clearly understood, I am afraid we will know no more of the mechanism of the action of gold. We have suggestive evidence that relapse may be associated with the elimination of gold. We do know that gold must be combined with a sulfhydryl group to be effective. This may have a bearing on its mechanism or it may be due solely to the fact that gold compounds, to be soluble at a pH around 7, must be in the gold-thiol form.

STUDENT: Is there any way to avoid toxic reactions?

DR. RAGAN: We believe that we can decrease the incidence of stomatitis by not exceeding a weekly dose of 50 mg. of the compound. Hemopoietic toxicity such as thrombocytopenia and agranulocytosis can be kept at a minimum by frequent blood counts with estimation of the platelets on the smear. Renal damage can be kept to a minimum amount by frequent urinalyses. The skin lesions are difficult to predict, some are preceded by an eosinophilia, some are not. All are preceded by a pruritus and at the first mention of pruritus, gold should be stopped. If the patient fails to develop a rash, we believe that by vigilance we may have avoided a severe dermatitis. However, most of the patients who develop pruritus go on to develop a rash of more or less severity even if the gold is stopped. We have a routine to which we adhere rather strictly. A patient receiving chrysotherapy has a white blood count with an estimation of platelets on the smear and a urinalysis every two to three weeks. I would again like to mention BAL, which promises to be fully as effective in combating gold toxicity as it is in arsenic and mercury poisoning.

DOCTOR: Do you believe that with adequate care, gold can be administered by the local medical doctor?

DR. BOOTS: We are somewhat reluctant to advocate the use of gold in general practice by physicians who have had no previous experience with it. Where we have sent patients from out of town back to their doctors with instructions on the administration of gold, we have found that more trouble developed than with patients we have followed ourselves. There are many alarums and excursions in the course of gold therapy and to evaluate these, it is important that the physician have considerable understanding of the eventualities which may develop. If a watch is kept over the blood count and urine and if gold is stopped at the first symptom of pruritus, sore mouth, or abdominal cramps, the physician who has not seen a lot of gold therapy should be able to carry out this form of treatment.

DR. RAGAN: The flexion contractures which develop in rheumatoid arthritis are a striking characteristic of the disease and the basis of many of the deformities. These, with the muscle atrophy and the micro-

scopic lesions in the muscle described by Freund, have led us to focus our attention on the skeletal musculature.

We have been fortunate in interesting Dr. Schlesinger of the Neurological Institute in this problem, and have asked him to discuss it for us today.

DR. E. B. SCHLESINGER: I have been asked to discuss the problem of muscle spasm in rheumatoid arthritis. There are few terms in clinical medicine which are so misused or which can evoke so much controversy as muscle spasm. We ought, therefore, first define our terms. Loosely, muscle spasm is a reflex defense phenomenon, a prolonged contraction not amenable to voluntary control, characterized by resistance to stretch and by diffuse, severe, poorly localized pain. How does this state come about? There are many possible mechanisms which may act as the initial stimulus. First, we may have actual irritation of the sensory nerve endings in the muscle mass itself. This may be due to mechanical trauma or inflammatory exudate. Secondly, muscle spasm may represent protective splinting of a neighboring joint which is the seat of disease. Lastly, the abnormal state of contraction may be secondary to changes in other parts of the neural arc, such as in the posterior columns, posterior root or sensory ganglion. Pathologic changes in these structures may lead to hyperesthesia, pain and diffuse tenderness in the muscle, which reacts by an attempt at shortening and immobilization.

All this may be worthy of further clarification. Normally, muscle stretch elicits afferent impulses arising in the muscle spindles. These impulses are conducted back to the cord, and a reflex contraction is then initiated by way of the motor side of the arc. This is the basic stretch reflex of Sherrington. When there is pathologic change somewhere in the system, there may be a potentiation of this cycle. The threshold of the arc is lowered, and the response becomes much more active than under normal circumstances. Thus we have the mechanism for a self-perpetuating circuit, the vicious cycle of pain and splinting or spasm. Attempted stretch elicits pain and further splinting, then more pain, and so on. Now that we have roughly defined the probable mechanism, we may turn to the problem at hand.

In acute rheumatoid arthritis, one is struck by the severity of the muscle changes. Here, in addition to joint inflammation (which causes reflex splinting) there may be infiltration of the actual muscle mass by inflammatory exudate. Also, there may be changes in the peripheral nervous structures themselves. Thus we find many of the elements which lead to muscle splinting or spasm and its accompanying pain and deformity. The acute arthritic limb adopts a flexion position which represents an attempt to avoid muscle stretching and joint irritation. These positions, a defense mechanism, may be easily reversible early, but if allowed to persist, may become a major cause of deformity. We know that long fixation leads to atrophy of disuse.

We must emphasize that in attempting to influence these phenomena, we are not attacking the primary disease entity but merely its secondary manifestations. Nevertheless, such changes may leave the patient crippled permanently, even though his primary disease be in complete remission.

How do we propose to handle such a situation? We know that any agent which acts by relieving pain or avoiding movement is useful in symptomatic relief. Any form of therapy which invades or breaks up the vicious cycle of pain and spasm may dramatically alter the clinical picture. Promotion of absolute rest has many dangers and needs no discussion here. Heat, analgesics, local anesthetic blocks, etc., are time-tried and respected forms of treatment. Unfortunately, none are specific or reliable.

In an attempt to attack the problem more basically, we have turned to drugs which

have a specific relaxant effect on muscle. Curare is such a drug. The initial difficulties in obtaining a suitable preparation being solved by the development of a long-acting suspension of curare in oil and wax, it is quite logical to try curariform drugs in an attempt to reduce reflex shortening with its concomitant pain. We have been using such a preparation in various syndromes which have in common the entity of muscle spasm. Our results are in the right direction but unquestionably open to criticism if any final conclusions were to be drawn so early in the work.

DOCTOR: What beneficial effects have you obtained with curare suspensions in oil and wax?

DR. SCHLESINGER: Our patients seem more comfortable. They show greater mobility. They do not adopt marked flexor protective positions. They may not require as much analgesia or sedation. They seem to respond better to physical therapy. These are all clinical impressions and therefore of little objective value. There are, however, objective data, too, which indicate a beneficial effect of curare. Perhaps the most important are electrical studies. Briefly, a muscle at rest shows no electrical activity when studied by standard electromyographic technics. A normal muscle can be put at rest in full extension. Certain of our patients with rheumatoid arthritis, on the other hand, show consistent evidence of electrical activity, incident to reflex shortening, except in positions of pronounced protective flexion. We believe we can claim a therapeutic response when such patients gain full extension and in that position show no bursts of impulses representing attempted shortening. Such results are obtained with curare. The patient you have seen today (Mrs. S.) is a good example of the desired end result.

Another objective criterion is obtained by a study of urinary creatine output. During his visit here, Dr. Mortensen of Denmark described to me his findings in a series of acute low back cases with severe muscle spasm. He was able to demonstrate a sharp rise in creatine output during the acute clinical phase and an abrupt fall in output when the clinical signs subsided. Adapting his technic to our problem, we have tried to study the changes which might occur in our patients with rheumatoid arthritis. There seems to be a rough correlation to date which may prove useful but much more work must be done.

DR. RAGAN: Gold is still a very controversial subject and curare is still new and experimental. However, there are certain broad concepts of treatment upon which I think almost everyone working in this field will agree and these should be stressed. Dr. Boots said he would talk about this part of the program.

DR. BOOTS: To state that we use chrysotherapy for rheumatoid arthritis often gives a wrong impression. It suggests that other forms of treatment have been discarded. Such is far from the truth.

Patients with early active disease are most suitable for gold therapy and best results are obtained in this group. Gold is discontinued immediately if any evidence of toxicity occurs. We do not like to administer gold to the elderly, to those with a history of liver or renal damage, or blood dyscrasia. Excellent results are not as frequent when the disease is advanced and marked deformities have occurred. Also, we hesitate to use gold for patients whose family physicians have advised strongly against taking it. We do not use gold if the disease is quiescent. For the reasons outlined, probably not more than 60 per cent of the patients with rheumatoid arthritis in our clinic are started on gold therapy and of this number 10 per cent receive inadequate gold treatment because of early development of toxicity. In addition to gold this group is treated with the more conservative measures which are used for the non-gold treated patient.

What are these other methods of therapy? They consist chiefly of (1) measures which improve the general health of the patient, reduce fatigue, giving him a chance for spontaneous remission, (2) measures which give symptomatic relief, and (3) the prevention and correction of deformities.

The time allowed will not permit of detailed discussion of all of these, and we will limit ourselves to little more than their enumeration.

MEASURES WHICH IMPROVE THE GENERAL HEALTH OF THE PATIENT

A. Rest (or avoidance of fatigue) is almost as necessary for rheumatoid arthritis as for tuberculosis. The amount varies from complete bed rest for the severely ill patient who has a persistent fever, to an hour's rest period before dinner, or the simple avoidance of severe fatigue for the mildly ill.

B. Nutrition. The patient is usually thin and undernourished, sometimes to the point of emaciation, and a highly nutritious diet is essential. We frequently supplement such a diet with 2 tablespoonfuls of cod liver oil at bedtime. While it would seem sensible to give an abundance of vitamins, massive doses of any particular vitamin seems to be of no specific value. In recent years, vitamin D in capsules of 50,000 units have been widely and, in our opinion, unjustifiably recommended in advertisements. In our experience such preparations have been of no proven value in rheumatoid arthritis and sometimes result in severe and irreversible vitamin D poisoning.

C. Treatment of Anemia. Hypochromic anemia is frequently present and responds poorly to iron administration. Several transfusions of 500 cc. of blood to such patients will usually cause marked improvement.

D. Removal of Intercurrent Infections. Formerly there was thought to be a direct relationship between rheumatoid arthritis and foci of infection. We have been unable to prove any such relationship. However, the eradication of infections, such as periapical abscesses and chronic sinus infections, helps the general health of the patient.

E. Climate. The prevalent opinion is that the disease rarely occurs in tropical climates. No well controlled experiment has ever been done of sending patients to the tropics but it would seem that this offers definite possibilities provided the patient can live as comfortably in such regions as in his home.

F. Psychotherapy. An optimistic attitude on the part of the physician is very helpful. These patients are easily depressed and it seems as though there is some relationship between their mental depression and increase in their symptoms.

MEASURES WHICH GIVE SYMPTOMATIC RELIEF

A. Analgesics and Sedatives. There is no proof that salicylates have any direct effect upon the course of rheumatoid arthritis but they offer considerable relief of the pain. Salicylates are of real value in giving the patient increased rest and comfort, and, as far as we can tell, do no harm.

B. Physiotherapy. Physiotherapy is of much more value for osteoarthritis than rheumatoid arthritis but it probably has no real effect upon the course of the latter disease. However, such measures as compresses or flaxseed poultices to a painful joint often offer relief.

PREVENTION AND CORRECTION OF DEFORMITIES

Much can be done by the internist in the prevention of contracture deformities by the use of posterior splints, applied for varying periods each day. These deformities are in large part due to muscle spasm and it may be that the use of curare in conjunction with exercises within pain limits as described by Dr. Schlesinger, will prove of equal value. The correction of deformities which have already occurred lies mostly in the

field of the orthopedic surgeon and will not be discussed at this time.

DOCTOR: I am not clear as to your opinions on the value of rest in the patient with rheumatoid arthritis.

DR. RAGAN: At the present time we believe that we cannot be too dogmatic upon this point. Rest has been one of the most trusted standbys in the treatment of rheumatoid arthritis and its value in diminishing pain, fever and evidence of activity of the disease process is unequivocal.

However, we believe that rest should be supervised. To tell a patient to go home to bed or to hospitalize a patient and prescribe strict bed rest can be very detrimental. The group at Cornell have shown that, in normal males with bed rest in a plaster spica, definite changes in the metabolism of the patient occur. Notably, a negative nitrogen balance sets in. Clinically, we know that muscle atrophy and osteoporosis are associated with continued inactivity. A patient with active rheumatoid arthritis confined to bed lies in a position of inactivity almost comparable to a body spica because of voluntary splinting of the painful joints. We believe that exercises within the limits of pain and fatigue can be carried out in such patients. In conjunction with adequate salicylate therapy to control pain and curarization to combat the element of muscle spasm the range of motion can be extended. This effort to decrease the muscle atrophy in rheumatoid arthritis is still in progress and a conclusive evaluation of the results cannot be made at this time but the preliminary results are encouraging.

SUMMARY

Rheumatoid arthritis is a common disease of unknown etiology, subject to remissions and exacerbations, characterized clinically by striking involvement of the joints and, to a varying degree of other systems, and demonstrated pathologically to be a disorder of connective tissue. Presenting certain common features with rheumatoid arthritis are serum sickness, rheumatic fever, disseminated lupus erythematosus, periarteritis nodosa and scleroderma. Despite clinical and pathological similarities, it is not implied that all these disorders have a common etiology.

The clinical picture of rheumatoid arthritis is well known. Cases are presented which serve to emphasize the multiplicity of systems involved as well as the overlapping of the other mesenchymal diseases in the clinical picture of rheumatoid arthritis.

Because the connective tissue appears to be the common denominator throughout this discussion, the nature of its two main subdivisions was considered. The three types of fibrous elements, collagenous, reticulin and elastic fibers are known to be denatured, insoluble proteins of high molecular weight. The cement substances on the other hand are made up of compounds or complexes of proteins with highly polymerized mucopolysaccharides. Hyaluronic acid, hyaluronosulfuric acid, chrondroitin sulfuric acid and the amyloid sulfuric acid ester are the only four polysaccharides yet identified. All are of high molecular weight and their exact composition is unknown. Specific enzymes called hyaluronidases exist in the mammalian body, as well as in many other natural sources, which possess the specific power of depolymerizing and hydrolizing hyaluronic acid and perhaps other polysaccharides. While all these substances are presumably concerned with the diseases under discussion, their normal physiology and pathological variations have not yet been worked out.

In some patients with rheumatoid arthritis, hyaluronate is increased in the synovial fluid but what significance this observation has remains to be determined.

When considered pathologically, rheumatoid arthritis presents two chief charac-

teristics. One is the granulomatous lesion of connective tissue with necrosis, round cell infiltration, palisading and giant cell reaction contributing to nodule formation. This may be grossly seen subcutaneously about the elbows or may be only microscopically visible in the connective tissues of nerves, blood vessels and muscle. The cther lesion is essentially the same but because it involves the connective tissues of joints—the synovial, capsular and subchondral tissues—results first in an acute inflammation and later in destruction of the joint. The clinical findings of redness, heat, swelling, pain, joint deformity, muscular spasm and atrophy, and subcutaneous nodules thus all have a common pathological basis. When this process is widespread the general manifestations of fever, weakness, anemia, weight loss, cardiac, renal, lymphatic and eye disease may also be understood.

Klinge has postulated that the initial lesion of rheumatoid arthritis involves the connective tissue cement substance. At the present time no etiological agent or mechanism is known. The hemolytic streptococcus theory has as yet resulted only in the diagnostic group A streptococcus agglutination reaction which is positive in about 55 per cent of cases of rheumatoid arthritis but which may be a non-specific reaction. As yet no virus etiology can be regarded as established nor has the possibility of allergy, bacterial or otherwise, though attractive, ever been placed on tenable grounds. Much of the difficulty lies in the fact that the disease as yet cannot be experimentally produced either in man or animal.

The problem of therapy is unsolved. The status of gold therapy is difficult to evaluate. Five to 10 per cent of patients develop early toxic reactions which preclude therapy. It may be possible to avoid stomatitis and renal damage by moderate dosage but the toxic reactions of the skin are unpredictable and not yet controllable. Ten to 20 per cent of patients receive no benefit from therapy. Forty to 60 per cent are definitely improved but of these 80 to 90 per cent relapse in a five-year period. Continuous treatment with gold to avoid these recurrences is now being tried.

It is believed that in the early cases of true rheumatoid arthritis, gold is the best means of therapy. In the Edward Daniels Faulkner Arthritis Clinic at the Presbyterian Hospital, about 50 per cent of patients with rheumatoid arthritis do not receive gold therapy either because of contraindications to gold therapy or because it is refused by the patient. About one-half of these show some improvement, whether due to the general measures instituted or to a spontaneous remission. Supportive measures include those directed at improving the general health of the patient: adequate rest, high vitamin and caloric diets, transfusions and the treatment or removal of intercurrent disease. They include psychotherapy to attempt to ease mental burdens and adjust the patient to his disease. Heat, salicylates and sedatives may make the acute stages less difficult while physiotherapy and appliances to prevent and correct deformities tend to improve the latter situations. Finally, because of the rarity of the disease in the tropics, the removal of the patient to the tropics should be considered where the status of the patient permits.

One interesting approach, novel but promising, is the use of curariform drugs. Based on the premise of a self-perpetuating vicious cycle of pain and muscle spasm initiated by reflex stimuli from diseased joints, muscle or the nervous reflex arc, a long-acting preparation of curare in oil and wax is employed to induce relaxation of muscle. Clinical improvement seems to follow and objective studies by electromyographic technics and creatine excretion, which are still being evaluated, tend to be corroborative.

Clinico-pathological Conference

Chronic Granuloma*

STENOGRAPHIC reports, slightly edited,† of weekly clinico-pathological conferences held in the Barnes Hospital are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, M. C., was a sixty-five-year old white male hotel executive, who entered the Barnes Hospital for the first time on February 12, 1946, complaining of generalized itching, cough and loss of weight. The family history was non-contributory. The patient stated that he had always been well until the onset of the present illness. Two years before entry he underwent bilateral inguinal herniorrhaphy without event. About eight months before admission he noted the onset of lacrimation which at times was intense; it was more pronounced on the left.

Six months prior to entry the patient developed a pruritic eruption on his legs. One month before admission the lesions became red and raised. The pruritus became generalized and so severe that the patient could not rest day or night. He was seen by a dermatologist who made a diagnosis of scabies but the lesions did not respond to specific treatment. Subsequently they resembled erythema multiforme and finally they took on the characteristic appearance of erythema nodosum. During the month before entry the patient noted increasing weakness and he felt feverish. His physician noted that he had temperature elevations as high as 101.6°F. on several occasions. During the six months before admission the patient lost 17 pounds. Two weeks before admission he had a sore throat which persisted for several days. Concomitantly the patient developed a cough which was productive of thick mucoid sputum. He had several profuse sweats and an occasional slight chill.

On physical examination at the time of entry, the patient's temperature was 37°C., pulse 90, respirations 18, and blood pressure 140/70. He was an elderly man who appeared pale and chronically ill. There were numerous excoriations on the skin. Over the lower extremities, and to a lesser degree over the upper ones, red, raised, tender nodules, 2 to 3 cm. in diameter, surrounded by a zone of erythema, were present. A few lymph nodes were palpable in the left posterior cervical chain and large, firm, freely movable nodes were felt in both axillary and inguinal regions and in the left epitrochlear region. There was chemosis of the right eye and the conjunctiva was inflamed. The left eye was similarly involved but to a lesser degree. The pupils reacted normally to light and accommodation. The right fundus appeared normal; the left could not be visualized. The left auditory canal was filled with green, foul-smelling débris. The drum was thick and no landmarks were visible. No perforation was seen. The nasal mucosa was reddened. The throat appeared normal. The epiglottis was red and thickened; the left vocal cord was fixed in the cadaveric position. The

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lungs were clear to percussion and auscultation. The heart was not enlarged; the rhythm was regular. A harsh, grade II systolic murmur was heard at the apex and at the aortic area. The liver was felt 2 cm. below the right costal margin; neither the spleen nor the kidneys were palpable. The physical examination was otherwise within normal limits.

Laboratory data were as follows: Blood count: red cells, 3,400,000; hemoglobin, 10.4 Gm.; white cells, 7,100; differential count: eosinophiles, 11 per cent; stab forms, 1 per cent; segmented forms, 67 per cent; lymphocytes, 21 per cent. Urinalysis: negative except for an occasional red blood cell per high power field. Stool examination: negative. Blood Kahn reaction: negative. Blood chemistry: non-protein nitrogen, 19 mg. per cent; total proteins, 7.7 Gm. per cent; albumin, 3.3 Gm. per cent; globulin, 4.4 Gm. per cent. Blood culture: no growth. Heterophile agglutination test: negative. Sputum examination: no tubercle bacilli seen. Bone marrow: stimulation of myeloid cells with a shift to the left; 7 per cent plasma cells and 2 per cent reticulum cells were present. Cephalin-cholesterol flocculation test: 1+. Roentgenogram of the chest: "The cardiac silhouette is within normal limits as is the aorta. There is a plaque of calcium in the aorta. Hilus shadows are quite prominent suggesting large lymph nodes. Lung markings are somewhat coarse and feathered; they extend out from the hilus on both sides. The parenchyma is clear." Gastrointestinal series: indeterminate. Cholecystogram: normal gallbladder. Electrocardiogram: slight notching was present and there was a Q wave in Leads I and IV; interpretation: myocardial damage.

During his hospital stay the patient's temperature rose daily, usually reaching 39°C. and occasionally 40°C. The pulse rate rose and fell consistently with the temperature curve; the respiratory rate was normal. Soon after admission, a lymph node was removed from the right axilla. The microscopic sections showed considerable hyperplasia of the lymphoid elements but the general architecture remained unchanged. A moderate number of eosinophiles was seen and there was some increase in fibrosis but no Dorothy Reed cells were visible. The epithelium was normal. A diagnosis of "reticular hyperplasia" was made.

The patient received repeated transfusions and was given a short course of roentgen therapy to the lymph nodes which gradually became smaller. The skin lesions varied in intensity but were never completely absent. Pruritus was a constant, distressing symptom. Shortly after admission, the patient's cough increased, and showers of crepitant inspiratory râles were heard at the base of the right lung. Penicillin therapy was given but the cough continued unabated. Many specimens of sputum were examined for tubercle bacilli but none were found. Numerous blood counts were not significantly different from those on admission except that the eosinophiles were reduced. Repeated cultures of the blood were sterile. A chest film taken about two months after entry showed considerable increase in the prominence of the hilar shadows on the right. The pulmonary markings were also accentuated in the right lung more than previously, and there was infiltration about the bronchial and vascular markings. Impression: "bronchopneumonia, right lung." The patient failed to improve, and on discharge he retained most of the symptoms present at the time of admission. He left the hospital on April 20, 1946.

He continued to do poorly at home; his fever persisted and the skin lesions did not improve. While at home he was given two injections of anti-reticular cytotoxic serum.

He reentered the Barnes Hospital on May 4, 1946.

At the time of entry, the patient's temperature was 38.3°C., pulse 90, respirations 24, and blood pressure 130/64. He appeared extremely ill; he was weak and emaciated. The skin was hot, generally atrophic and slightly icteric. Areas of brown pigmentation were noted over the trunk at the site of previous lesions. On the forearms there were several small movable nodules with slight surrounding erythema. One was present on the dorsum of the left hand. There were also pustules scattered over the skin. The auricle of the left ear was somewhat swollen, red and tender to the touch. Moderate contracture deformities at the elbows and knees were present. There was no significant lymphadenopathy. The eyelids were slightly swollen; the palpebral conjunctivae were pale and small pin-point yellow papules were present on their surface. Examination of the lungs revealed dullness to percussion, bronchial breath sounds and medium râles at the right base posteriorly. There was a soft, grade II systolic murmur at the apex. The liver edge was felt 4 cm. below the right costal margin. The spleen was not palpable. Neurological examination showed flattening of the right side of the face. The tendon reflexes were all hyperactive.

Laboratory studies were as follows: Blood count: red cells, 3,360,000; hemoglobin, 10.7 Gm.; white cells, 6,850; differential count: eosinophiles, 1 per cent; stab forms, 13 per cent; segmented forms, 55 per cent; lymphocytes, 28 per cent; monocytes, 3 per cent. Urinalysis: albumin, trace; sediment, occasional white blood cell per high power field. Stool examination: negative. Coccidioidin skin test: negative. Culture of skin pustules: non-hemolytic staphylococcus; cultures for fungi were negative.

The patient received anti-reticular cytotoxic serum and transfusions. His temperature ranged between 38°C. and 40°C. The skin manifestations noted on entry persisted; in addition, lesions characteristic of erythema nodosum recurred. A decubitus ulcer developed over the coccyx. A fluctuant, subcutaneous mass was noted in the left axilla from which thick pus was aspirated. The patient was discharged unimproved on June 1, 1946.

Because of the investigations on the treatment of lymphomas with nitrogen mustard compounds at another university clinic, the patient was transferred to that institution. There the physical findings were identical with those recorded on the patient's last Barnes Hospital admission.

Studies were as follows: Blood counts: unchanged from those noted previously. Total proteins, 7.1 Gm. per cent; albumin, 2.1 Gm. per cent; globulin, 5.0 Gm. per cent. Cultures of skin lesions for fungi: negative. Roentgenogram of the chest: "Enlargement of both hilar shadows, extensive pulmonary infiltration in both lungs, more on the right."

The skin lesions were biopsied and the sections were studied by several pathologists. No definite diagnosis was made but an "atypical lymphoma" seemed most likely. Because the diagnosis could not be definitely established, therapy with a nitrogen mustard derivative did not seem justified. The patient was given iodides with some improvement in the appearance of the skin lesions. He was discharged and returned immediately to the Barnes Hospital where he was admitted for the last time on July 5. 1946.

At the time of entry the patient's temperature was 39.2°C., pulse 130, respirations 40. He was emaciated, pale, and appeared *in extremis*. There was slight icterus of the sclerae. The skin was atrophic and large areas of brown pigmentation were noted. Numerous ulcerations including the decubitus over the coccyx were present. The

tongue was red and dry. Signs of fluid were noted at the right lung base. Otherwise the physical findings were unchanged from those of the previous admission.

Laboratory data included the following: Blood count: red cells, 2,830,000; white cells, 2,750; differential count: eosinophiles, 2 per cent; stab forms, 38 per cent; segmented forms, 37 per cent; lymphocytes, 19 per cent; monocytes, 4 per cent.

The patient failed rapidly and died on July 6, 1946, twenty-four hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: This case presented such a difficult problem that despite very thorough study a definite diagnosis could not be made during the patient's long illness. Four aspects of the illness were most prominent; first, the distressing pruritus and several skin lesions; second, the persistent fever; third, the lymphadenopathy; and finally, the hyperglobulinemia. Dr. Weiss, would you comment on the skin lesions and their relation to the underlying disease?

DR. RICHARD S. WEISS: I first saw this man in January, 1946. He complained of extreme pruritus but the skin lesions at that time were not striking. The only finding was the presence of excoriations which in some respects resembled those seen in scabies. The distribution of the lesions, however, was not typical of scabies. Nevertheless, I prescribed anti-scabetic treatment; the patient returned in one week and stated that he was very much better. He then developed urticaria and lesions characteristic of erythema multiforme. Subsequently erythema nodosum was noted. Several weeks later when I again saw him, he looked quite ill and complained bitterly of pruritus. His temperature was slightly elevated and there was alarming lymphadenopathy which led me to the conclusion that the patient had a serious systemic disease, possibly Hodgkin's disease or one of the lymphomas. I therefore recommended that he be hospitalized for more detailed study.

DR. HAROLD SCHEFF: It is of interest that a differential blood count done at that time showed a 10 per cent eosinophilia.

DR. ALEXANDER: Do you attribute the eosinophilia to the skin manifestations, Dr. Weiss?

DR. WEISS: Eosinophilia occurs in many generalized skin diseases. In cases of lymphoma with involvement of the skin the eosinophilia is usually more profound than was recorded in this instance.

DR. ALEXANDER: It may be concluded, I presume from your observations, Dr. Weiss, that the patient definitely exhibited the lesions of erythema multiforme and erythema nodosum. Attention has been called to the fact that the patient had generalized lymphadenopathy and one of the nodes in the right axilla was removed for study. Dr. Moore, would you describe the microscopic sections cut from the surgical specimen.

DR. ROBERT A. MOORE: The first lantern slide (Fig. 1) shows a section of the skin removed. The thickness of the epidermis was approximately normal. There was slight edema of the dermis about the blood vessels and about some of the accessory structures of the skin not shown in the section. A cellular infiltration, consisting largely of the cells of the mononuclear series, was noted. The diagnosis on the basis of these findings was chronic inflammation of the skin. The second slide (Fig. 2) is that of a section of the lymph node; it shows the capsule of the node with the associated vascular and lymphatic spaces. There was hyperplasia of the follicles of the node, but the cellular types present within the node were normal, and there was only slight cellular infiltration of the capsule. The pathologic diagnosis was hyperplasia and chronic in-

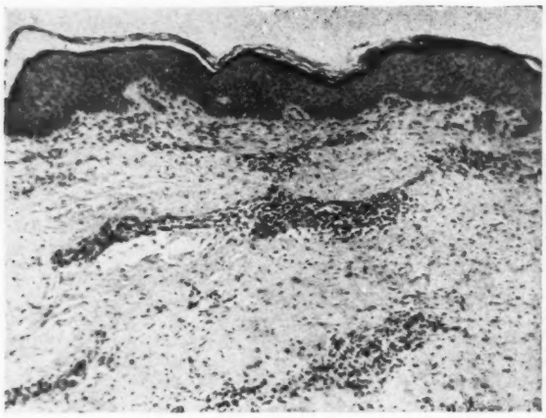

FIG. 1. (No. 46-1194). Microscopic section of skin removed at the time of lymph node biopsy. The changes are those of chronic inflammation. × 47.

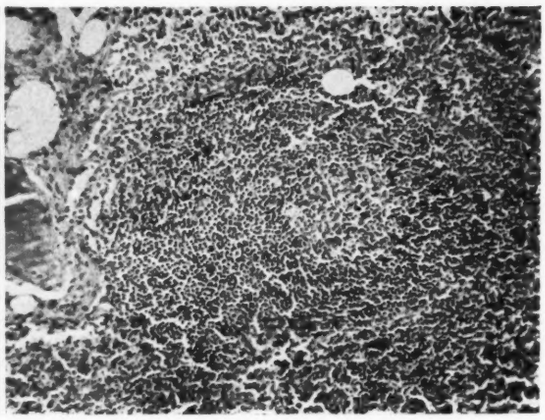

FIG. 2. (No. 46-1193). Microscopic section of lymph node showing follicular hyperplasia. × 47.

flammation of the lymph node. In neither the skin nor the lymph node were there any changes characteristic of a specific disease entity.

DR. ALEXANDER: From the information available, Dr. Moore, do you believe that the diagnosis of lymphoma is likely?

DR. CARL V. MOORE: It is our opinion that either reticulum cell sarcoma or Hodgkin's disease was the most likely possibility. Against the former was the fact that the lymph node did not show characteristic changes; against the latter was the fact that the patient never had a lymphopenia. Although there is no definitive blood picture in Hodgkin's disease, frequently a lymphopenia is noted during some phases of the disease.

DR. ALEXANDER: Is it true that in Hodgkin's disease a leukocytosis may occur?

DR. C. V. MOORE: That is correct. The white cell count may range from a leukopenic level to counts of 150,000 or more.

DR. ALEXANDER: The bone marrow was reported as showing stimulation of the myeloid elements. Would you comment on the significance of this finding.

DR. C. V. MOORE: Myeloid stimulation such as was observed here is compatible with almost any inflammatory disease.

DR. ALEXANDER: If this patient had one of the lymphomas, for example lymphosarcoma, would the lymph nodes be expected to show characteristic histologic changes.

DR. EDWARD H. REINHARD: Yes, they would. However, I have seen instances in which the first lymph node biopsies from patients with lymphosarcoma or with Hodgkin's disease failed to show definitive lesions whereas subsequent biopsies showed the characteristic histological changes. In lymphosarcoma, however, there is usually tremendous proliferation of the lymphocytes with destruction of the architectural pattern and, very frequently, invasion of the capsule.

DR. ALEXANDER: Is it correct to say that frequently in Hodgkin's disease the characteristic lesions may not be seen in lymph nodes in certain phases of the disease whereas in lymphosarcoma, if there is lymphadenopathy, pathologic changes in the lymph nodes will be present in most cases.

DR. REINHARD: I think that is correct.

DR. ALEXANDER: Therefore, in this case, if a diagnosis of lymphosarcoma cannot be made from the microscopic sections of the lymph node removed from the patient's axilla, it may be inferred that in all probability the patient did not have lymphosarcoma. Dr. Moore, do you feel that the diagnosis of Hodgkin's disease is still tenable despite the lymph node findings?

DR. C. V. MOORE: Yes.

DR. ALEXANDER: The skin lesions were consistent with Hodgkin's disease. The fever was persistent for many many months. If there is high fever in Hodgkin's disease, is it necessarily of the Pel-Ebstein type or may it be continuous?

DR. C. V. MOORE: The fever is not continuous as a rule, but it may be.

DR. ALEXANDER: Would you agree that the blood picture and bone marrow findings do not suggest leukemia?

DR. C. V. MOORE: They most certainly do not.

DR. ALEXANDER: Dr. Scheff, you and Dr. Womack saw giant cells in the microscopic sections of the lymph node. Did you think that the findings in the section were compatible with a diagnosis of tuberculosis of the lymph nodes?

DR. SCHEFF: We did not think so.

DR. ALEXANDER: Dr. Goldman, would you comment on generalized lymphadenopathy in tuberculosis. Is there an adenopathic type of generalized tuberculosis, and if so, is it common?

DR. ALFRED GOLDMAN: Generalized lymphadenopathy does occur in generalized tuberculosis but it is not very common.

DR. ALEXANDER: Dr. Bottom, did the chest roentgenogram indicate to you that this patient had tuberculosis?

DR. DONALD S. BOTTOM: He has had tuberculosis, but I believe the present findings are indicative of a quiescent tuberculous lesion in the lungs.

DR. ALEXANDER: Does generalized adenopathy as a manifestation of tuberculosis occur in any particular age group?

DR. GOLDMAN: It may occur in patients at any age, but it usually occurs in patients in the younger age groups.

DR. ALEXANDER: It would be quite rare, then, in a patient as old as this one.

DR. GOLDMAN: Yes. That is one of the reasons why Hodgkin's disease seems more likely in this case. However, some of the findings are compatible with sarcoidosis and that diagnosis should be considered. Generalized lymphadenopathy is common in sarcoidosis.

DR. ALEXANDER: The apparent enlargement of the hilar lymph nodes is also in keeping.

DR. GOLDMAN: I am not able to state whether the skin lesions seen in this patient are compatible with Boeck's sarcoid. Perhaps Dr. Weiss would discuss that point.

DR. WEISS: The skin lesions were not consistent with those seen in sarcoidosis. Usually the skin manifestations of sarcoid are moderately hard, flat plaques or nodules; they have no tendency to suppurate and they are usually situated adjacent to the joints.

DR. ALEXANDER: Are there other features in this case suggestive of sarcoidosis?

DR. W. BARRY WOOD, JR.: The eye findings certainly should be mentioned.

DR. ALEXANDER: That is a good point. We have no specific information about the uveal tract, but the eye signs were prominent in the clinical course.

DR. WOOD: In the cases of sarcoid described by Dr. Longcope, the initial symptoms were frequently related to the eye. That was true in this case. Further, it has been emphasized by many writers that the serum globulin tends to be extremely high in sarcoid, and I think that the hyperglobulinemia here is another point in favor of Dr. Goldman's suggestion. Against the diagnosis of sarcoid, however, is the relatively malignant course of this patient's illness. I would therefore postulate that if the patient had sarcoid, he probably had tuberculosis, too; the two diseases are not infrequently seen together at postmortem examination.

DR. ALEXANDER: Tuberculosis involving what organs?

DR. WOOD: I cannot specify where Dr. Moore will find the tubercle bacilli, Dr. Alexander, but I think active tuberculosis would explain the relatively rapid course of

the illness; sarcoid alone without tuberculosis usually runs a more benign course.

DR. ALEXANDER: Am I clear, then, that you believe the patient had both sarcoid and tuberculosis rather than tuberculosis alone.

DR. WOOD: Yes, I think that such a combination is likely in this case.

DR. ALEXANDER: Certainly sarcoid and tuberculosis occur together frequently; indeed some writers believe that they are the same disease.

DR. WOOD: Dr. Futcher followed some of the cases of sarcoid in Baltimore, and I would like to ask him whether or not pruritus was a prominent feature.

DR. PALMER H. FUTCHER: I do not recall that it was.

DR. ALEXANDER: When sarcoid is complicated or followed by tuberculosis, does the tuberculous process occur at the site of the sarcoid lesion, or do they occur apart from one another?

DR. ROBERT A. MOORE: I belong to the group which believes that sarcoid and tuberculosis are two independent diseases. My answer to the question, therefore, would be that although tuberculosis may occur in a patient with sarcoid, the sarcoid lesions do not become tuberculous.

DR. ALEXANDER: Dr. Reinhard, would you discuss the anti-reticular cytotoxic serum which this patient received.

DR. REINHARD: Anti-reticular cytotoxic serum is prepared by immunizing animals—horses or rabbits—with a mixture of human bone marrow and lymph node or spleen. The serum presumably contains antibodies against human reticulo-endothelial cells. Bogomolets, who developed the serum, claims that small amounts stimulate the reticulo-endothelial tissues of the body, whereas larger doses are destructive. He advocates the use of the serum as a means of avoiding the changes of senility, and also in treating diseases of the reticulo-endothelial system; in the latter he advises larger doses in order to destroy those tissues.

DR. ALEXANDER: Would you comment on the clinical experience with the serum.

DR. REINHARD: There have been extremely few clinical results reported; most investigations to date are reported in the Russian literature. In this country there is confirmatory evidence, from experimental work, that the serum does have a potent antibody which will affect the growth of reticulo-endothelial cells in tissue culture.

DR. ALEXANDER: Is it generally available?

DR. REINHARD: No. We obtained it from a commercial laboratory which supplies it for investigational use only, and we were told very little about the method of preparation. We were told only how much of the serum to give, at what interval to give it, and that the treatment should not be repeated in less than six weeks.

DR. ALEXANDER: What about experience with the nitrogen mustard compounds in Hodgkin's disease and other lymphomas?

DR. REINHARD: The evidence published to date indicates that the nitrogen mustards have a definite beneficial effect in Hodgkin's disease and perhaps in other lymphomas. The remissions which are induced by nitrogen mustards do not last as long as those following *x*-ray, and the compounds are certainly at least as damaging to other normal structures as *x*-ray; I believe that most of the investigators who are studying the nitrogen mustards now feel that they may be useful in cases resistant to *x*-ray. However, one should emphasize that such patients rapidly become resistant to nitrogen mustard also.

In regard to the diagnosis, Dr. Alexander, either a fungus infection or tuberculosis seem very strong possibilities to me.

DR. ALEXANDER: The possibility that this patient was afflicted with a fungus infection was entertained very seriously. Cultures were made on Sabouraud's media

but were unrevealing. Likewise coccidioidin skin tests were done. In regard to tuberculosis I should like to ask if erythema multiforme occurs commonly in tuberculosis.

DR. WEISS: Not commonly, but it is seen occasionally.

DR. ALEXANDER: It has been taught that when one sees erythema nodosum, one must think of rheumatic fever or tuberculosis. Actually, erythema nodosum may be seen with a variety of infections.

DR. ROBERT ELLIOTT: It has been pointed out that uveo-parotid fever may be one of the manifestations of Boeck's sarcoid; however, I believe that erythema nodosum is not common in sarcoidosis.

DR. PAUL O. HAGEMAN: It seems to me that there are two points supporting the diagnosis of neoplasm in this case; one, the paralyzed vocal cords; and two, lymph nodes which receded with *x*-ray therapy. These two points lead me to favor the diagnosis of Hodgkin's disease.

DR. CARL V. MOORE: Dr. Alexander, a thorough search was made for acid-fast organisms in this man's sputum and none was found. Likewise the bone marrow preparations were examined for acid-fast organisms with negative results. I would like to ask whether the lymph nodes were stained for acid-fast organisms.

DR. SCHEFF: No, they were not.

DR. ALEXANDER: In summary, it may be said that there appears to be little unanimity of opinion among the staff as to the diagnosis. Hodgkin's disease was considered the most likely diagnosis when the patient was in the hospital and is still favored by some. Others have expressed the opinion that the patient was suffering from tuberculosis or Boeck's sarcoid or possibly from both. We have apparently been unable to assemble conclusive evidence in favor of any one of these possibilities. We are forced, therefore, to ask the pathologists to enlighten us as to the correct diagnosis.

PATHOLOGIC DISCUSSION

DR. ROBERT A. MOORE: From the gross findings the diagnosis at the time of the autopsy was a granulomatous disease involving particularly the right lung, and to a lesser extent, the liver, the spleen and the porta-hepatic lymph nodes. The real problem, therefore, was to identify the nature of this granulomatous process. Examination of the microscopic sections was necessary to determine the diagnosis. Figure 3 shows a section of one of the nodules in the lung. The lesion is distinctly granulomatous; there is necrosis in the center and in some areas there is caseation. Surrounding some of the nodules fibrosis is seen and there is an occasional giant cell about the edge of the nodule. There are epithelioid cells with finely vacuolated cytoplasm in the periphery. Essentially normal pulmonary tissue lies adjacent to the nodule.

In Figure 4 another nodule is seen with greater magnification. There is necrosis in the center of a group of epithelioid cells; at the periphery, fibrosis is developing. There are numerous capillary vessels in the young proliferating fibrous tissue. An acid fast stain showed acid-fast bacilli at the center of the necrotic foci in the lungs and other organs.

Figure 5 is a section of the surrounding lung showing a mononuclear exudate in the alveoli and proliferation within the alveolar wall. In other words there was a tuberculous pneumonia about the granulomatous lesion in the right lung.

In Figure 6 a section of a tracheobronchial lymph node is seen; there is complete caseation of the central part of the lymph node with slight cellular infiltration in the capsule. This type of lesion in a tracheal-bronchial lymph node is seen in first-infection tuberculosis. In other words, there is massive caseation of the lymph node extending to the capsule with a sharp line of

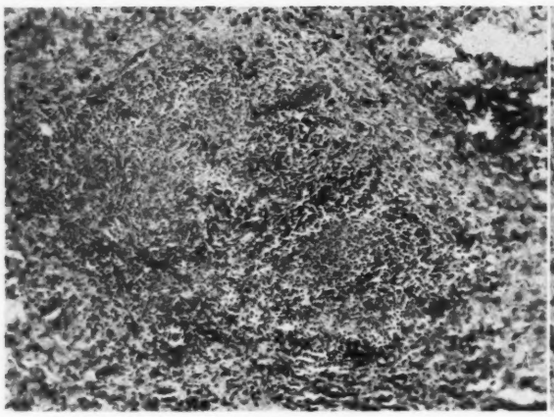

FIG. 3. (No. 46-1204). Microscopic section of a pulmonary nodule showing necrosis and caseation with peripheral fibrosis. × 47.

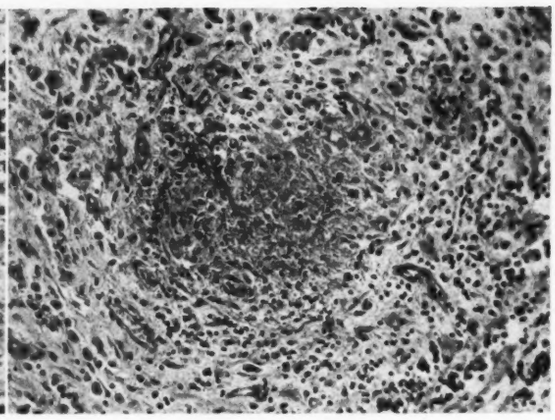

FIG. 4. (No. 46-1197). Microscopic section of a pulmonary nodule under higher magnification. Note the central necrosis and peripheral fibroblastic and capillary proliferation. × 97.

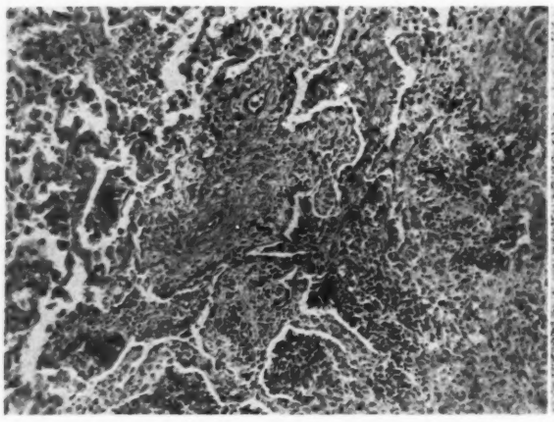

FIG. 5. (No. 46-1198). Microscopic section of an area in the right lung showing a mononuclear exudate. × 47.

FIG. 6. (No. 46-1196). Microscopic section of a tracheobronchial lymph node. Note central caseation and the sharply demarcated fibrous tissue capsule. × 47.

demarcation between the fibrous tissue of the capsule and the caseous lymphoid tissue.

Figure 7 pictures a section of the spleen showing a similar necrotic granulomatous lesion in the splenic pulp. Here, in contrast with the pulmonary lesions, there is practically no reaction about the focus of necrosis, no epithelioid cells and no fibrosis, but the necrotic area extends directly to join the splenic pulp. There were acid fast-bacilli in the necrotic nodules. Thus, in the lung, in the spleen and in the liver there was necrosis of tissue and the lesion was of the type described as necrotizing tuberculosis. The tubercles were necrotic rather than caseous. Under higher magnification the character of the necrosis could be seen; numerous strands of fibrin permeated the necrotic areas. In caseous tuberculosis threads of fibrin are not seen.

Sections of the pericardium indicated that it was involved by the tuberculous process; so-called lymphocytic tubercles were identified in the pericardium.

In Figure 8, another variant of the reactions of tuberculosis is seen; the section is taken from one of the ulcers in the skin of the thorax. A blood vessel is shown; it is thickened in parts because of edema and because of cellular infiltration. Such a lesion with the marked intimal proliferation is representative of tuberculous granulation

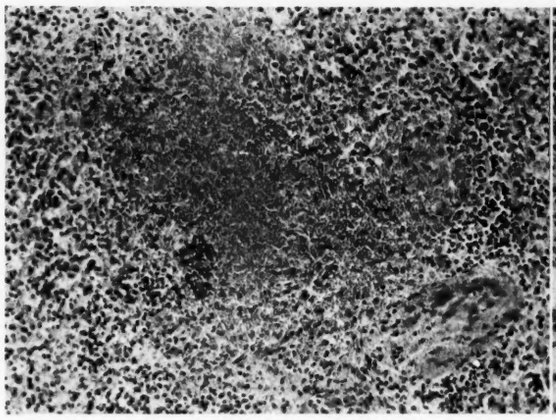

FIG. 7. (No. 46-1199). Microscopic section of nodule in spleen showing necrosis and absence of cellular reaction about the focus. × 47.

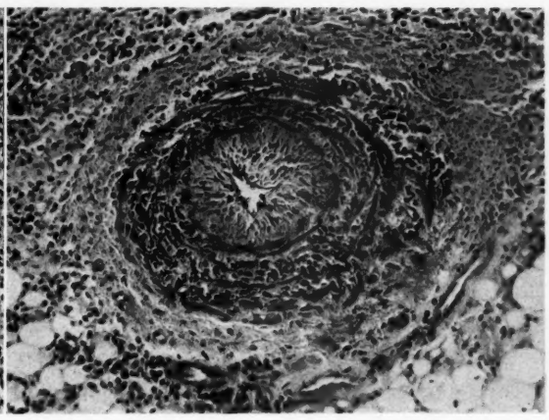

FIG. 8. (No. 46-1202). Microscopic section from a skin lesion showing characteristic reaction of a blood vessel in tuberculosis.

tissue. Characteristically, it is seen in the meninges and may at times be the only histologic evidence on which the diagnosis of tuberculosis is based. The lesion is not frequently seen in other viscera.

The bone marrow showed hyperplasia, particularly of the red cell series, but there were no granulomatous lesions in the marrow; it is understandable, therefore, that no acid-fast bacilli were found in smears of the marrow. In the testis there was hemorrhage into the interstitial tissue and atrophy of the seminiferous tubules; the latter change occurs in patients suffering from chronic debilitating disease. The spermatogonia and the cells of the spermatogenic series were entirely absent; the centers of the seminiferous tubules were filled with cells of the Sertoli type, and the basement membrane was greatly thickened and appeared edematous.

It is apparent from the description, both gross and microscopic, that the patient had granulomatous lesions in which acid-fast bacilli were demonstrated and of which the histologic structure was consistent with a diagnosis of necrotizing tuberculosis. To reconstruct the exact clinical course of this patient is difficult. Apparently he had a first infection tuberculosis as evidenced by the calcified nodules in the *x*-ray film of the chest; he also had re-infection tuberculosis as demonstrated at the autopsy by fibrous scars at both apices. About six months before entry, either the tuberculosis was reactivated from the fibrous scars or the patient acquired a new infection. The process went on for some time in reasonable equilibrium and the patient did not become critically ill until three to five weeks before his death. At that time the lesions took on another character; they became necrotizing in type, causing vascular spread and a rapidly fatal course.

There was no evidence in the sections of any additional disease such as sarcoidosis. All of the nodules that were observed were characteristic of tuberculosis.

Final Anatomical Diagnosis. Fibrous scars of the apices of the lungs; caseous and necrotizing tuberculosis of all lobes of the right lung; pleural effusion (right 1,500 cc., left 50 cc.); caseous and necrotizing tuberculosis of the tracheobronchial lymph nodes; necrotizing tubercles in the liver, porta-hepatic lymph nodes, spleen and right pleural surfaces; tuberculosis of skin with ulceration and secondary suppurative inflammation; localized areas of reddish discoloration of skin; desquamation of skin of trunk and extremities; "lymphoid tubercles" in the pleura-pericardium, and atrophy of the testis with focal hemorrhages.

Case Reports

Extensive Polycystic Disease of the Kidneys and Liver*

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POLYCYSTIC kidney disease has been extensively studied both in this country and abroad. It is reported to occur at autopsy approximately in the proportion of 1 to 500 cases. An exhaustive and excellent study of this condition was made by G. D. Oppenheimer in 1934,[1] and E. T. Bell[2] in 1935. Polycystic liver disease is less frequently encountered. A detailed study of this condition was made by L. Severi[3] in 1937.

Polycystic disease is believed to be a congenital affection. Individuals afflicted with it usually develop gradually increasing renal insufficiency and die with the symptoms of uremia. Tetany has not been often mentioned as a complicating feature. The following case is of interest in this respect. It is also of interest because of the extensive involvement of the liver.

CASE REPORT

A forty-four year old housewife was admitted to the Lebanon Hospital to the service of Dr. David Greenberg on October 5, 1937, complaining of weakness, headache, vertigo, dragging sensation in the abdomen and nocturnal attacks of pain and spasm in the toes and fingers. The family history was essentially negative and outside of a herniorrhaphy four years ago, there were no previous illnesses. She was married and had four children; all four pregnancies and deliveries were normal and uneventful. There was amenorrhea for the past three months.

The patient was apparently well until about six months prior to admission when she began to experience the gradual onset of weakness, headache and dizziness. Three months prior to admission she began to complain of being awakened at night with severe attacks of pain, spasm and cramps in the toes and fingers. She also felt a dragging heavy sensation in the abdomen, and complained of pyrosis, eructations, habitual constipation and "palpitation of the heart" with attacks of precordial pain. She lost no weight. There were occasional bouts of jaundice lasting from one to three days. Physical examination revealed slight jaundice, marked venous pulsations in the neck, systolic murmur over the base, blood pressure 118/80, a markedly enlarged liver which reached to the level of the umbilicus; the edge was hard and nodular but not tender; the spleen was enlarged, its edge was smooth and not tender.

Roentgen examination of the gastrointestinal tract disclosed an irregularity in the stomach which was interpreted as an organic lesion in the pars media of the stomach; *x*-ray of the chest was negative; *x*-ray of the genitourinary tract showed a large and ptosed right kidney; the left renal outline was visualized. Intravenous pyelogram revealed filling of the pelvis and calyces of the left kidney but there was an absence of the opaque media in the pelvis and calyces of the right kidney. During cystoscopy no urine could be obtained from the left side and the dye did not appear from either orifice in half an hour. The total phenolsulphonthalein excretion was 2 per cent. The specific gravity of the urine was fixed between 1.008 and 1.012 with an average daily output of 1,200 cc. It contained 1 plus albumin but no sugar. Microscopic examination showed occasional white and red blood cells. Blood count: red blood cells, 3,200,000; white blood cells 5,800; polymorphonuclears 72 per cent; lymphocytes 22 per cent; mononuclears 1 per cent; basophils 1 per cent; platelet count, coagulation and bleeding

* From the Laboratory of Lebanon Hospital, New York City, N. Y.

time were normal. The hemoglobin was 55 per cent (Sahli). Gastric analysis showed no free hydrochloric acid the total acidity being 10; there was no free hydrochloric acid after histamine injection. The basal metabolic rate was 0; stools were negative for occult blood. Blood chemistry findings are shown in Table 1. Temperature and pulse were always normal. Because of the *x*-ray findings in the stomach a diagnostic laparotomy was performed. The stomach was normal but the liver was found to be cystic. Biopsy of the liver showed congenital polycystic disease of the liver.

TABLE 1

	1st Admission	2nd Admission	3rd Admission
Non-protein nitrogen	120	204–162	255–300
Urea nitrogen	98	90	
Serum protein	5.2	8.5	6.7
Albumin	2.4	3.8	3.6
Globulin	2.8	4.7	3.1
A/G ratio	.86	.81	1.2
Icteric index	6	7	
Total cholesterol	155	.....	194
Cholesterol esters	69	.....	79
Phosphorus	9.5		
Phosphatase	2.1 (Bodansky)		
Calcium	8.4		

The postoperative course was uneventful and the patient was discharged with some improvement on November 23, 1937. She felt fairly well and had no complaints until May, 1938, when her symptoms of heartburn, vomiting, constipation and dizziness recurred. She was re-admitted to the hospital on June 4, 1938. At this time blood chemistry showed increased retention of nitrogenous waste products. (Table 1.) There was urobilin in the urine. The patient developed an infectious dermatitis during her stay in the hospital which was treated symptomatically. She showed some improvement; the non-protein nitrogen fell to 162 mg. per cent, and she was discharged on June 29, 1938.

She was re-admitted on September 22, 1938, with the symptoms of moderate uremia. She now was emaciated, the skin was bronzed and she appeared acutely ill. The liver edge was nodular and hard; its edge was felt at the level of the umbilicus. Both kidneys were palpable; there was no ascites. On admission the hemoglobin was 45 per cent (Sahli); red blood cells 3,160,000; white blood cells 11,000; polymorphonuclears 80 per cent; lymphocytes 12 per cent; mononuclears 6 per cent; non-segmented polymorponuclears 2 per cent. There was achromia, aniso- and poikilocytosis. The specific gravity of the urine was fixed between 1006 and 1008, and it contained 2 plus albumin and pus clumps. Blood chemistry showed increased retention of nitrogenous waste products. (Table 1.) The total non-protein nitrogen rose to 300 mg. per cent on September 28, 1938. The patient expired on October 6, 1938.

Autopsy: Only the kidneys and liver are described. Both kidneys were enlarged; their vertical diameters measured approximately 25 cm. Their surfaces were markedly irregular and were studded with variously sized cysts. The capsule stripped with moderate difficulty. (Figs. 1 and 2.) On section, the cut surfaces appeared irregularly honey-combed by the cross section of numerous variously sized cysts separated in most places by narrow strips of parenchyma or, in many places, only by their opposing walls. Most of the cysts contained a straw-colored serous fluid; some of the cysts contained a sanguineous turbid fluid, while still others were filled with a gelatinous homogeneous mass. The pelves were somewhat dilated, the ureters were patent. The microscopic appearance of the organ was that of variously sized cysts, many of which were markedly dilated. The smaller of these cysts were lined by low cuboidal epithelium which resembled that of collecting tubules, while the larger cysts were lined by a very markedly flattened epithelium. The cysts were filled with a pale pink staining amorphous material in which were seen red blood cells and cellular débris; other cysts, in addition, contained a purulent exudate. Among the cysts there were seen considerable areas of functioning kidney parenchyma. In these areas moderate numbers of fairly well preserved glomeruli were found which showed a mild degree of congestion, a moderately increased cellularity of the epithelium with beginning hyaline changes and edema. The tubules were irregular and most of them markedly dilated. Their epithelial walls were flattened and showed moderate to marked degrees of degenerative

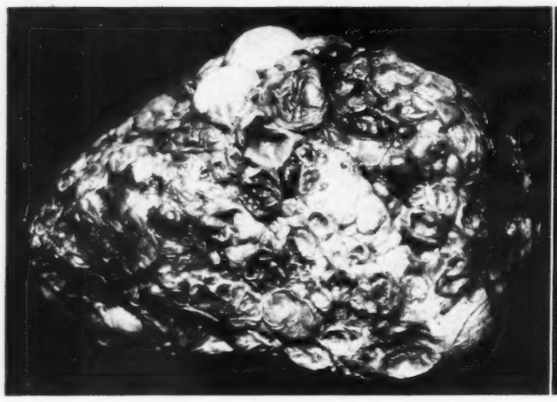

FIG. 1. External surface of polycystic kidney. Note the closely packed cysts which vary in shape, size and depth.

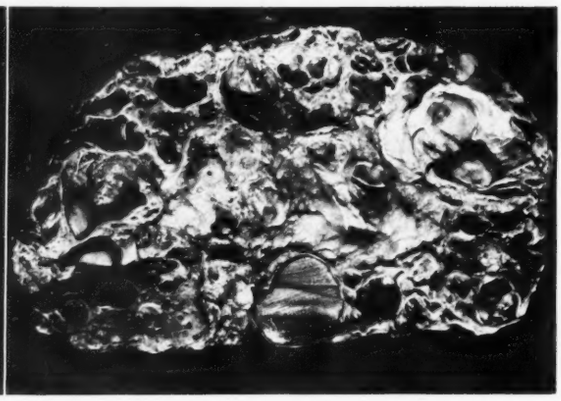

FIG. 2. Cross section of polycystic kidney. Note the almost complete replacement of kidney tissue by the various sized cysts.

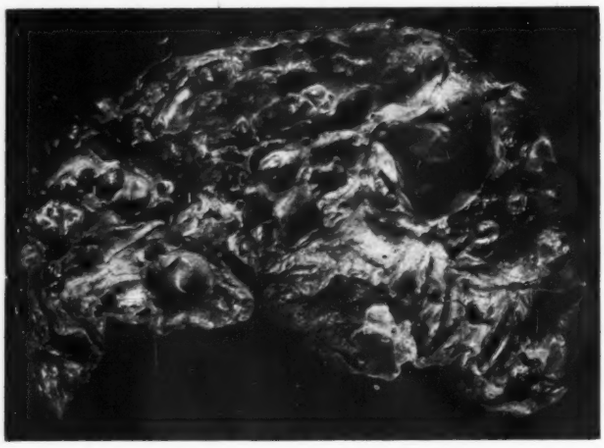

FIG. 3. Cross section of polycystic liver. Note the close resemblance to the cross section of the kidney.

changes. The interstitial connective tissue was markedly increased and, in most places, it was infiltrated by mononuclear cells. There was also a moderate degree of congestion present throughout. The blood vessels showed only minimal sclerotic changes; most of them appeared normal.

The liver weighed 4,200 Gm. and extended to about one finger above the umbilicus. The surfaces were irregularly nodular with cysts which varied in size from a few millimeters to 5 to 10 cm. in diameter. The diaphragmatic portion of the right lobe was the only part of the liver which was found to be relatively free of cysts. On section (Fig. 3) the cut surfaces resembled those of the kidneys and were also irregularly honey-combed by the cross sections of cysts most of which contained a clear serous fluid, while others contained a turbid brown fluid or a gelatinous homogeneous mass. In the relatively uninvolved portions, the liver parenchyma presented a fairly normal appearance. The gallbladder and biliary tracts appeared normal. Microscopically, sections through the uninvolved portions showed normal liver architecture; there was a moderate degree of edema and the cytoplasm of the liver cells showed granular degeneration; the nuclei, however, were fairly well preserved. The portal fields seemed to be less prominent than seen normally. Sections taken from the cystic area showed numerous variously sized cystic cavities. The smaller of these were lined by low cuboidal epithelium resembling that of the bile ducts, while the larger cysts were lined by a markedly flattened epithelium. The cysts contained pale pink amorphous substance; there was no bile pigment seen in them. Some of these cysts were filled with a polymorphonuclear exudate and there was a similar infiltration in the adjacent

liver parenchyma surrounding them. The larger cysts were surrounded by a thickened fibrous wall. The liver tissue in between these cystic areas showed all grades of degenerative changes.

COMMENT

This case presented several noteworthy features. It is interesting to note that with such extensive involvement of both kidneys and liver, this patient was able to lead a fairly normal existence up to a few months prior to her death. This ability to carry on in spite of these serious handicaps seems to depend upon two factors: First, the uninvolved portions of the kidneys and liver parenchyma undergo hypertrophy and partially compensate for the tissue destroyed by the cysts. This compensatory mechanism is especially marked in youth and early adult life. With advancing age, however, this ability is gradually decreased; the cysts on the other hand, continue to enlarge, gradually replacing the persistent islands of functioning tissue. As a result, the destruction of the latter goes on more rapidly than it can be replaced by compensatory hypertrophy and the patient progresses toward renal or liver insufficiency and death. The second factor in maintaining a normal existence is the ability of the organism to adjust itself and to acquire an increased tolerance to the accumulation of waste products in the blood. Another interesting feature of this case was the low blood pressure. Throughout the patient's stay in the hospital during the three admissions the blood pressure never rose above 118/80. This may be explained by the fact that the vessels of the kidney showed little or no sclerotic changes. It is now generally recognized that hypertension occurs in cases in which there is serious interference with the blood supply of the kidneys as shown by the well known experiments of Goldblatt[4] who was able to produce hypertension in dogs by partially clamping the renal arteries.

The third feature of interest was the development of tetany. Symptoms of tetany have been observed to occur in cases of chronic nephritis. This is usually explained by the fact that due to the decreased ability of the kidney to excrete inorganic salts there is an accumulation of inorganic phosphates in the blood; with this the calcium is decreased since it has been shown that the relationship between these two elements tends to be reciprocal. The consequent development of hypocalcemia and the decrease in the serum calcium/phosphorus ratio is believed to play a significant rôle in the precipitation of clinical symptoms of tetany.[5]

The irregularity in the body of the stomach as revealed by *x*-ray was probably produced by pressure of the encroaching cysts of the left lobe of the liver upon the walls of the stomach. This was erroneously interpreted as a gastric neoplasm.

SUMMARY

1. A case of extensive polycystic disease of the kidneys and liver is reported in a forty-four-year old housewife.

2. There was no hypertension in spite of the extensive involvement of both kidneys.

3. The symptoms of tetany in this case were attributed to the increase of inorganic phosphates in the blood with a concomitant development of hypocalcemia and decrease in the serum Ca/P ratio.

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Mycotic Lung Infection*

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LUNG cysts are liable to infection. A case seeming to illustrate this is herein reported:

CASE REPORT

Mr. C. G. was admitted, at the age of fifty-five, to the Mount Morris Tuberculosis Hospital in May, 1937. He had been a glass cutter all his life. The past history was non-contributory, except that he had "pleurisy" every year for the past ten years. In February, 1937, he contracted a cold, followed by a cough which became productive, and increasing weakness. *X*-ray in an itinerant clinic revealed a cavity at the right apex, with light infiltration at the left apex and he was admitted to this hospital.

Significant findings were limited to the chest, where on the right side there was dullness to the second rib and sixth dorsal spine. Breath sounds were roughened and crackling râles were audible above the clavicle and the fifth dorsal spine. On the left, an occasional râle was heard over the apex. *X*-ray films confirmed the clinic films. The patient was raising 3 to 4 ounces of odorless, mucopurulent sputum. A blood study revealed nothing except leucocytosis and eosinophilia of 6 per cent, and sputum studies failed to reveal tubercle bacilli, fungi or Vincent's organisms. His temperature was subfebrile. The cough was paroxysmal and violent, especially when the patient was in the recumbent position. Bronchoscopy revealed inflammation of the right upper lobe bronchus.

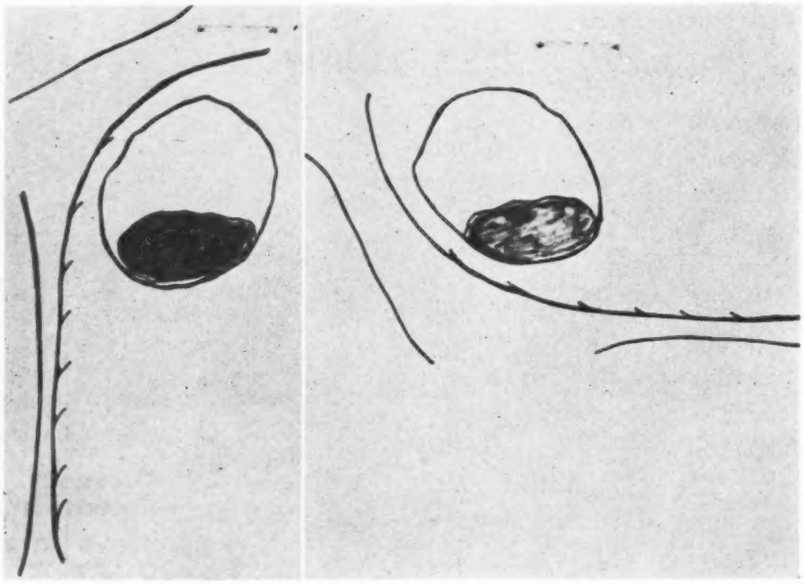

FIG. 1. FIG. 2.

FIGS. 1 and 2. Sketches of the right apex in the erect anteroposterior (Fig. 1) and right lateral recumbent (Fig. 2) illustrating diagrammatically movement of the intracavitary mass with change in position.

X-ray films taken in January, 1938, in various positions revealed that there was a loose body in the cavity which shifted with change of

* From the Mt. Morris Tuberculosis Hospital, Division of Tuberculosis, New York State Department of Health.

position. This body was roughly circular, about 3 cm. in diameter, and could be seen to gravitate freely in a cavity three times as large. (Figs. 1 and 2.) On February 16, 1938, operation by a posterior approach disclosed an irregular cavity containing inspissated material having a mousy odor. This cavity had several bronchial communications. After adequate drainage, myoplasty was done to close the cavity and obliterate the bronchocutaneous fistulas. The patient was discharged from the hospital February 11, 1939, cured. Eosinophilia on discharge was 3 per cent.

A section of the thick cavity wall revealed "a zone of fibrotic tissue with marked necrosis of the inner layer. All layers are infiltrated with eosinophils." Neither yeast, molds, fungi nor tubercle bacilli were seen.

The cavity contents were shown by microscopic examination to be mycotic material of the aspergillus group. Attempts were made to identify the organism more definitely but all cultures failed to grow.

Follow-up on November 7, 1944, revealed that the patient has been working as a glass cutter and is apparently well.

COMMENTS

The occupational history of glass cutting, involving the use of carborundum and pulverized sand, for forty years, confused the picture, as did the presence of some infiltration at the left apex, interpreted as being tuberculosis. The exact mechanism involved in the condition described is obscure. It is suggested that there was a lung cyst or emphysematous bleb at the right apex. This sustained an aspergillus infection, which then died, leaving a thick-walled cavity containing a mobile, putty-like mass of dead organisms. This mass sometimes acted as a ball-valve over the bronchial fistulas causing the severe paroxysmal cough.

Editorial

Venous Catheterization

Advances in medicine depend on the development of new methods. It is easy to think of things that one would like to know. It is more difficult to outline a problem for which methodology to give the needed information is available. Interest in cardiovascular research has been greatly stimulated by the demonstration of South American investigator[1] and by the group at Bellevue Hospital that a radiopaque catheter can be safely introduced into the venous system through an incision in a superficial vein.[2,3] Once in the vein, the catheter may be guided under the fluoroscope into the jugular vein, the right atrium, the right ventricle or the pulmonary artery. It may be passed down through the right atrium into the inferior vena cava and on out into the hepatic or renal veins. In patients with atrial septal defect, the catheter may enter the left side of the heart. In patients with a ventricular septal defect, the catheter may be passed into the aorta.

This method has had immediate clinical application in the diagnosis of certain types of heart disease. High right ventricular pressure is present in patients with cor pulmonale.[4] The presence of certain types of shunts can be demonstrated by study of the oxygen content of samples of blood drawn from different chambers of the heart.[5,6] These diagnostic methods are of great interest because of the recent advances in cardiac surgery.

Venous catheterization has opened a wide field of investigation in the field of cardiac dynamics. The lesser circulation can now be studied and many questions concerning the control of blood flow through the lungs will be answered in the near future. The data obtained on the relations between atrial pressure and ventricular filling will lead to a better understanding of the factors controlling the cardiac output.

A method for measuring the hepatic blood flow using the technic of hepatic vein catheterization has recently been described.[7] Studies on the metabolism of the kidney are now possible as methods are available for obtaining both the renal blood flow and the renal arteriovenous oxygen difference.[8]

At least 1,500 persons have been subjected to this procedure in the last four years. Thrombosis at the site of the incision in the antecubital vein occurs occasionally. There have been no serious complications. It seems safe to predict that venous catheterization will become an accepted technic in many hospitals.

Eugene A. Stead, Jr., M.D.

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Book Review

THIS small, inexpensive volume,* "A Primer for Diabetic Patients," contains a surprising amount of practical information for the diabetic patient which should lead to his informed cooperation in management.

The first five chapters contain brief simple discussions of diabetes, the urine tests, the insulins, the complications of diabetes and their remedies. The last four chapters, comprising more than half the book, are devoted to foods and diets and are sufficiently detailed to permit anyone of average intelligence to plan palatable menus of known composition. Questions at the end of each chapter are designed to emphasize the important points covered.

While the value of the "Primer" is undisputed, and its popularity attested to by the number of editions published, certain minor criticisms may perhaps be ventured. The insistence that in general not more than twenty units of protamine zinc insulin should be used in one day seems a trifle conservative. Perhaps more stress is placed on weighing foods and learning their substitution value in a standard diet than teaching their composition and actual caloric equivalents. The height-weight-age tables at the back of the book are in type so small as to be difficult to read.

However, these are hardly serious objections. Otherwise, the clarity and detail of the presentation, the excellence of the typography and the handy pocket-sized format make the "Primer" prescribed reading for every diabetic.

F. K. H.

* A PRIMER FOR DIABETIC PATIENTS. By Russell M. Wilder, M.D., PH.D., F.A.C.P. Eighth edition reset. Cloth. Pp. 192 with 8 illustrations. Philadelphia, 1946. W. B. Saunders Company. *Price* $1.75.

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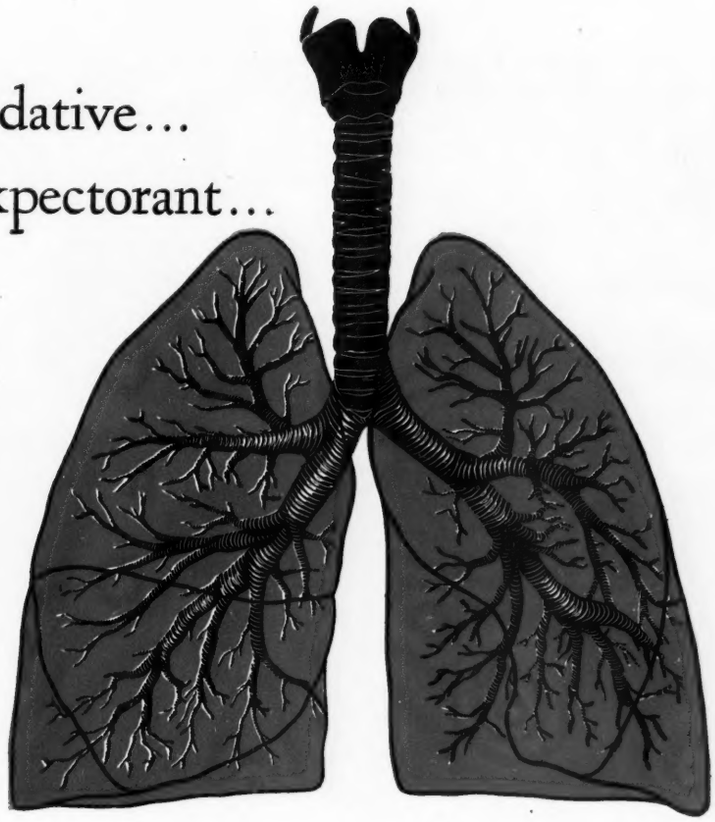

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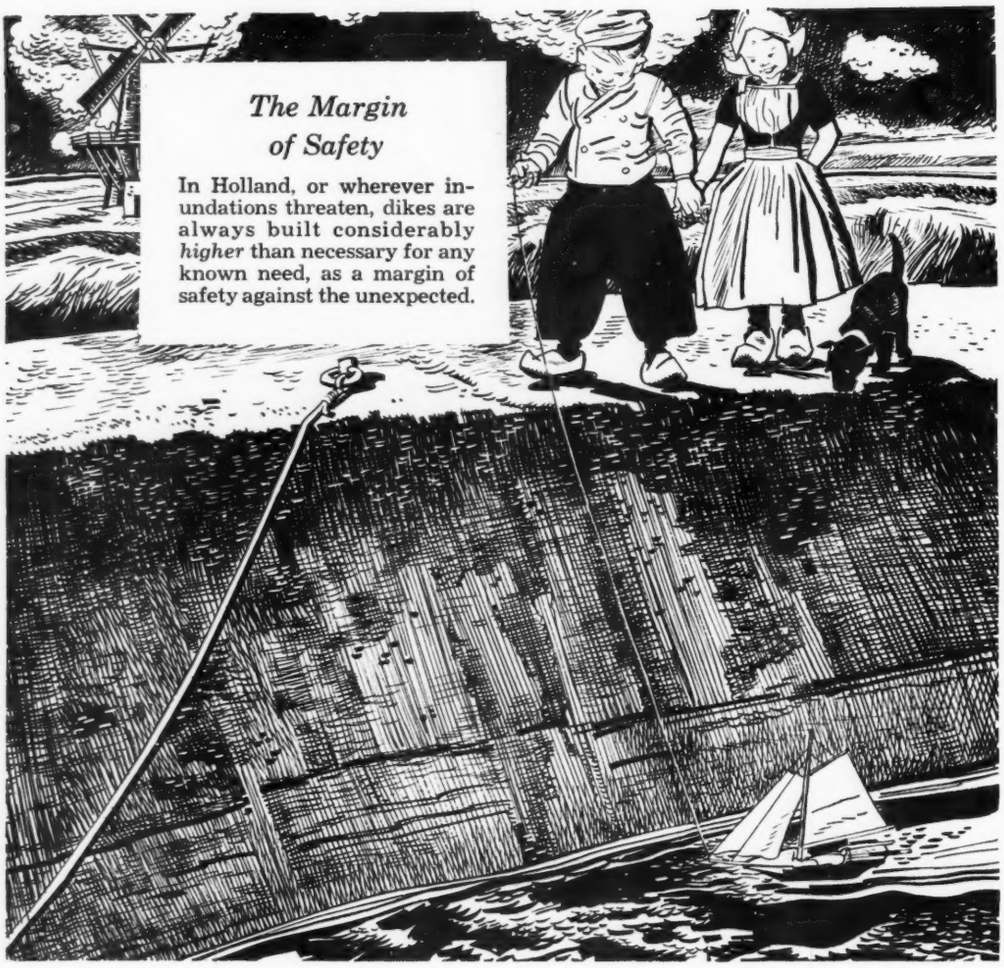
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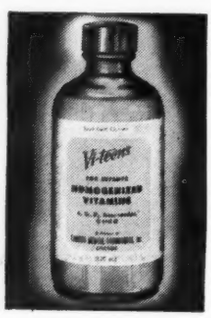

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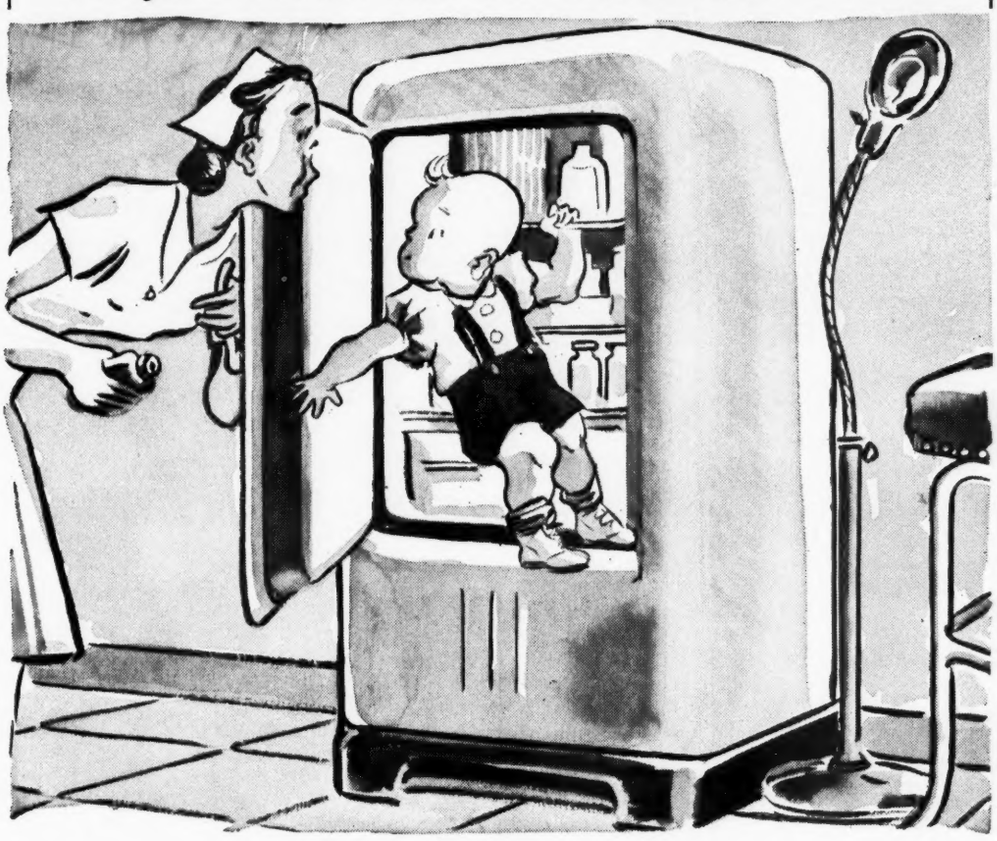

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